Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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R10933-10987-COV-2069

This supplement contains the following items:

Clinical Study Protocol

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-Cov-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2

Compound:	REGN10933+REGN10987
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[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
E (protein)	Envelope protein
EAP	Efficacy assessment period
ECG	Electrocardiogram
ED	Emergency department
EDC	Electronic data capture
ELF	Epithelial lining fluid
EOS	End of study
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	independent Data Monitoring Committee
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFIA	Lateral flow immunoassay
M (protein)	Membrane protein
mAb	Monoclonal antibody
MERS-CoV	Middle East respiratory syndrome coronavirus
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
PCSV	Potentially clinically significant value
RBC	Red blood cell
RBD	Receptor binding domain
Regeneron	Regeneron Pharmaceuticals, Inc.
RT-PCR	Reverse transcription polymerase chain reaction (test)
RT-qPCR	Quantitative reverse transcription polymerase chain reaction (test; refers to the central lab testing in this protocol)

S	Spike protein of the SARS-CoV-2 virus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UCC	Urgent care centers
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2
Site Location(s)	Multiple sites in the United States (US) and other countries
Principal Investigator	TBD
Objectives	For analysis of endpoints, there are 2 defined cohorts based on the subjects' SARS-CoV-2 infection status at baseline, as measured by central lab SARS CoV-2 RT-qPCR (quantitative reverse transcription polymerase chain reaction): negative (cohort A) or positive (cohort B). A strict definition of COVID-19 signs and symptoms will be utilized for the primary endpoint, which include: fever PLUS ≥1 respiratory symptoms (sore throat, cough, shortness of breath), OR 2 respiratory symptoms, OR 1 respiratory symptom PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise). A broader definition including the signs/symptoms in the strict definition and additional symptoms will be used for secondary endpoints (23 terms: Feverish, Sore throat, Cough, Shortness of breath/difficulty breathing, Chills, Nausea, Vomiting, Diarrhea, Headache, Red or watery eyes, Body aches such as muscle pain or joint pain, Loss of taste/smell, Fatigue, Loss of appetite, Confusion, Dizziness, Pressure/tightness in chest, Chest pain, Stomach ache, Rash, Sneezing, Runny nose, Sputum/phlegm). Objectives are for subjects who are seronegative at baseline (by central lab test) unless noted. **Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline** ***Cohort A Primary Efficacy Objectives*** • To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (strict-term) confirmed by RT-qPCR • To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR ***Cohort A Primary*** **Safety Objective** • To evaluate the safety and tolerability of REGN10933+REGN10987 following subcutaneous (SC) administration compared to placebo ***Cohort A Secondary*** **Objectives** • To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR • To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic SARS-CoV-2 infection confirmed by RT-qPCR

- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR test results
- To evaluate the impact of REGN10933+REGN10987 compared to placebo
  - On health care utilization
  - On absenteeism from daily responsibilities
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected pharmacokinetic (PK) parameters.
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following subcutaneous (SC) administration in seropositive subjects
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects

Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline

***Cohort B Secondary* Objectives**

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing development of:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR test results
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 and selected PK parameters in serum
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration in both seronegative and seropositive subjects

	• To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects • in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects
Study Design	This is a phase 3 randomized, double-blind, placebo-controlled study in adults with household contact exposure to individuals with SARS-CoV-2 infection in geographic areas with an active COVID-19 outbreak. All subjects in the study will be household contacts with sustained close exposure (at least 48 hours) with an individual with SARS-CoV-2 infection (index case) but who are themselves asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening. Randomization will be performed by individual study subjects, not by households. Approximately 2000 subjects will be enrolled. **Screening/Baseline (day 1)** Randomization will be performed on an individual subject basis, however all subjects randomized will be given a household identification number in the case that multiple members of the same household are enrolled and receive study drug. This ensures that correlation among subjects within the same household may be considered in the statistical analysis. Randomization will be performed by site and stratified for assignment of treatment group by test results of local molecular diagnostic assay for SARS-CoV-2 from respiratory samples (positive, negative, or unavailable) and on-site LFIA serology assay (seropositive, seronegative, or unavailable), and age group (≥50 or <50) (yes vs no). Cohort allocation will be based on central lab baseline SARS-CoV-2 RT-qPCR for data analysis: cohort A (negative) and cohort B (positive). Statistical analyses will be conducted separately in each cohort which will be based on central lab determination of viral positivity and serological status. Subjects will be randomized in a 1:1 allocation ratio to 1 of 2 treatment groups (placebo or REGN10933+REGN10987 [1200 mg (600 mg of each mAb SC]). This study will be preceded by safety review of data from other studies: a safety sentinel group of 30 patients with COVID-19 dosed with REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 8000 mg IV or placebo in the leading phase 1 studies of REGN10933+REGN10987 in the treatment of COVID-19 patients. Randomization in this study will not begin until the Independent Data Monitoring Committee (IDMC) for the treatment studies provides "study may proceed" conclusion from the IV dosing sentinel group. **Sentinel Group (day1 to day 4)** Enrollment in this study will be carried out in 2 phases: Sentinel group of approximately 30 subjects, irrespective of allocation to cohort A or cohort B, pooled between this study and the accompanying pre-exposure prophylaxis study in in at-risk subjects [R10933-10987-COV-2068]. 1. Subjects will be monitored for safety on-site for a minimum of 4 hours after administration of the first dose of study drug and then daily via visits to the study site or phone calls for the first 4 days (96 hours). Because REGN10933+REGN10987 will already have cleared a sentinel safety

group at higher doses administered IV, the sentinel group in this study will focus on safety evaluation for injection site reactions and hypersensitivity reactions, and data will be reviewed before progressing with enrollment of additional study subjects. The blinded safety data review will be led by a designated member of the Regeneron clinical team (generally either the medical monitor or the clinical trial manager) and at a minimum the data review team will include the Regeneron Medical Monitor, Study Biostatistician, Risk Management Lead or designee, and the Senior Vice President of Early Clinical Development & Experimental Sciences.

2. Following a conclusion of the blinded safety data review that the study may proceed, the study will resume enrollment.

After subjects provide informed consent, they will be assessed for study eligibility. The screening visit and randomization visits occur on the same day. Prior to randomization, a local molecular diagnostic assay for SARS-CoV-2 RT-PCR from respiratory sample and local serology assay for anti-SARS-CoV-2 will be performed. The results of these assays will be used as stratification factors for randomization to treatment groups (placebo or REGN10933+REGN10987). Nasal swab and saliva samples for central lab testing of SARS-CoV-2 RT-qPCR and blood sample for central lab serology will also be collected and sent to central lab on the same day as collection. On day 1, after completing baseline assessments and sample collection, all subjects will receive a single-dose of study drug.

Efficacy Assessment Period (day 1 to day 29)

Efficacy, safety, sample collections, and other study assessments will be performed at specified time points throughout the efficacy assessment period (EAP). If subjects are able to travel and can do so while maintaining social distancing guidelines, site visits may be possible; alternatively, mobile units or home health nurses may be utilized. Throughout the study, biological samples will be obtained by adequately trained and delegated study personnel at study locations where appropriate personal protective equipment (PPE) are available to be used.

At each weekly visit, nasal swab and saliva samples will be collected for SARS-CoV-2 RT-qPCR to be tested at a central lab. The investigator or designee will contact each subject weekly (site visit or telemedicine) to assess the subject's general health, and to document all AEs in general, and any signs and symptoms associated with SARS-CoV-2 infection since the last contact.

Any subject who develops fever, an acute respiratory illness or other symptoms that they feel could be related to COVID-19 should alert the study staff immediately. If the investigator or designee suspects SARS-CoV-2 infection, both nasal swab and saliva samples should be collected and sent for central lab testing. The subject may also be asked to provide a blood sample if it correspnds to a scheduled visit (according to the Schedule of Events).

Subjects with laboratory confirmed SARS-CoV-2 infection during the EAP should be informed as soon as possible and should undergo medical isolation to prevent contact with others to reduce the risk of further transmission. Since the subjects will likely be isolated, assessments and sample collections may occur through a variety of methods.

For all subjects who have a confirmed SARS-CoV-2 infection, they will continue to be tested (sample collection weekly) until 2 confirmed negative SARS-CoV-2 RT-qPCR test results are achieved. This testing may continue through the EAP and into the Follow-up period.

Subjects presenting with acute illness should be medically managed according to local standard of care as per the discretion of the treating physician.

	If a subject is hospitalized for suspected SARS-CoV-2 infection, every effort should be made by the site personnel to collect, as soon as possible, nasal swab and/or saliva samples for central lab SARS-CoV-2 RT-qPCR testing. **Follow-up Period (day 30 to day 226)** Subjects who remain SARS-CoV-2 RT-qPCR negative throughout the EAP will complete the end of the EAP and enter the Follow-up Period to be followed for 7 months. Subjects who become SARS-CoV-2 RT-qPCR positive during the EAP will continue to have weekly nasal swab and saliva samples for SARS-CoV-2 RT-qPCR testing until 2 confirmed negative SARS-CoV-2 RT-qPCR test results are achieved at least 24 hours apart, even after they complete the EAP and enter the study Follow-up Period to be followed for 7 months. In such situations, these visits for sample collection should be characterized as unscheduled visits. At each scheduled visit, the investigator or designee will contact each subject (site visit or telemedicine) to assess and document the subject's general health, AEs in general and signs and symptoms associated with SARS-CoV-2 infection since the last contact, as described for the EAP
Study Duration	For each subject, there are 3 study periods: a 1-day screening/baseline period, a 1-month EAP, and a 7-month follow-up period after the end of the EAP.
End of Study Definition	The end of study is defined as the date the last subject completes the last study visit, withdraws from the study, or is lost to follow-up.
Population	
Sample Size:	**Cohort A:** Approximately 1700 adult subjects with a negative rapid SARS-CoV-2 RT-PCR at baseline will be enrolled. **Cohort B:** Approximately 300 adult subjects with a positive rapid SARS-CoV-2 RT-PCR at baseline will be enrolled.
Target Population:	Asymptomatic, healthy adults who are household contacts to an individual with a positive SARS-CoV-2 RT-PCR assay (index case)
Treatments	
Study Drug	REGN10987 and REGN10933
Dose/Route/Schedule:	1200 mg (600 mg of each mAb) /SC / single dose on day 1
Placebo	Matching solution
Route/Schedule:	SC / single dose on day 1
Endpoints	Endpoints are specified for study cohorts. Symptomatic SARS-CoV-2 infection is determined by a positive central lab SARS-CoV-2 RT-qPCR result during the EAP with signs/symptoms occurring within ±14 days of a positive RT-qPCR. The definition for "strict-term" and "broad-term" signs/symptoms of SARS-CoV-2 infection is presented earlier in Objectives. The endpoints are for subjects who are seronegative at baseline (based on central lab test), unless otherwise noted.

Primary:	**Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline** ***Cohort A Primary Efficacy Endpoints*** • Proportion of subjects who have a positive SARS-CoV-2 RT-qPCR (based on central lab test) and signs and symptoms (strict term) of SARS-CoV-2 infection within the efficacy assessment period (EAP). • Proportion of subjects who have a positive SARS-CoV-2 RT-qPCR confirmed infection (based on central lab test) during the EAP. ***Cohort A Primary Safety Endpoint*** • Proportion of subjects with treatment-emergent adverse events (TEAEs) and severity of TEAEs
Secondary:	**Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline** ***Cohort A Secondary Efficacy Endpoints*** • Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad term) during the EAP • Proportion of subjects who have a positive SARS-CoV-2 RT-qPCR and the absence of signs and symptoms (strict term) during the EAP • Proportion of subjects who have a positive SARS-CoV-2 RT-qPCR and the absence of signs and symptoms (broad term) during the EAP • Number of days of symptomatic SARS-CoV-2 infection (strict-term) from the first day of the first sign or symptom until the last day of the last sign or symptom associated with the first positive SARS-CoV-2 RT-PCR that occurs during the EAP • Number of days of symptomatic SARS-CoV-2 infection (broad-term) from the first day of the first sign or symptom until the last day of the last sign or symptom associated with the first positive SARS-CoV-2 RT-PCR that occurs during the EAP • Time-weighted average of viral shedding ($\log_{10}$ copies/mL) from the first positive SARS-CoV-2 RT-qPCR in nasal swab sample (that has an onset during the EAP) until 22 days after the positive test during the EAP • Time-weighted average of viral shedding ($\log_{10}$ copies/mL) from the first positive SARS-CoV-2 RT-qPCR in saliva sample (that has an onset during the EAP) until 22 days after the positive test during the EAP • Maximum SARS-CoV-2 RT-qPCR $\log_{10}$ viral copies/mL in nasal swab samples among individuals with ≥1 RT-qPCR positive that has an onset during the EAP • Maximum SARS-CoV-2 RT-qPCR $\log_{10}$ viral copies/mL (saliva samples) among individuals with ≥1 RT-qPCR positive that has an onset during the EAP • Area under the curve (AUC) in viral shedding ($\log_{10}$ copies/mL) from the first positive SARS-CoV-2 RT-qPCR in nasal swab samples until the first confirmed negative test, that has an onset during the EAP • Area under the curve (AUC) in viral shedding ($\log_{10}$ copies/mL) from the first positive SARS-CoV-2 RT-qPCR in saliva swab samples until the first confirmed negative test, that has an onset during the EAP • Number of medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP

- Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Number of days missed for daily responsibilities, including work (employed adults) or school (matriculating students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP

Cohort A Secondary Safety Endpoints

- Proportion of baseline seropositive subjects (based on central lab test) with TEAEs and severity of TEAEs
- Incidence and severity of symptomatic SARS-CoV-2 infection in seronegative and seropositive subjects (based on central lab test) in both the EAP and follow up period

Cohort A Pharmacokinetic and Immunogenicity Endpoints

- Concentrations of REGN10933+REGN10987 in serum over time and selected PK parameters in both seronegative and seropositive subjects (based on central lab test)
- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933+REGN10987 over time in both seronegative and seropositive subjects (based on central lab test)

Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline

Cohort B Secondary Efficacy Endpoints

- Proportion of subjects who subsequently develop signs and symptoms (strict term) of symptomatic SARS-CoV-2 during the EAP within 14 and 28 days of a positive RT-qPCR
- Proportion of subjects who subsequently develop signs and symptoms (broad term) of symptomatic SARS-CoV-2 infection during the EAP within 14 and 28 days of a positive RT-qPCR
- Number of days of symptomatic SARS-CoV-2 infection (strict-term)
- Number of days of symptomatic SARS-CoV-2 infection (broad-term)
- Time-weighted average change from baseline in viral shedding ($\log_{10}$ copies/mL) in nasal swab samples until day 23.
- Time-weighted average change from baseline in viral shedding ($\log_{10}$ copies/mL) in saliva samples until day 23
- Area under the curve (AUC) in viral shedding ($\log_{10}$ copies/mL) in nasal swab samples until the first confirmed negative test
- Area under the curve (AUC) in viral shedding ($\log_{10}$ copies/mL) in saliva swab samples until the first confirmed negative test
- Maximum SARS-CoV-2 RT-qPCR $\log_{10}$ viral copies/mL in nasal swab samples

	• Maximum SARS-CoV-2 RT-qPCR $\log_{10}$ viral copies/mL in saliva samples • Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection • Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection • Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection • Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection • Number of days missed for daily responsibilities, including work (employed adults) or school (matriculating students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection ***Cohort B Secondary Safety Endpoints*** • Proportion of subjects with treatment-emergent adverse events (TEAEs) and severity of TEAEs in both seronegative and seropositive subjects (based on central lab test) • Incidence of symptomatic SARS-CoV-2 infection as evidence to monitor ADE, in seronegative and seropositive subjects (based on central lab test) in both the EAP and follow up period ***Cohort B Pharmacokinetic and Immunogenicity Endpoints*** • Concentrations of REGN10933+REGN10987 in serum over time and selected PK parameters in both seronegative and seropositive subjects (based on central lab test) • Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933+REGN10987 over time in both seronegative and seropositive subjects (based on central lab test)
Procedures and Assessments	**Screening/Baseline Procedures:** The following procedures will be performed for the purpose of determining study eligibility or characterizing the baseline population: demographics (eg, age, sex, race, weight, height, etc), medical history, local molecular diagnostic assay for SARS-CoV-2 from respiratory samples, and onsite serum serology for anti-SARS-CoV-2 (IgG/IgM by lateral flow immunoassay [LFIA]), and query for risk for SARS-CoV-2 infection. Local molecular diagnostic assay for SARS-CoV-2 from respiratory samples: the investigator or sub-investigator will verify that the subject tests negative or positive for local molecular diagnostic assay for SARS-CoV-2 and record the local test result in the eCRF, specimen type (eg, nasal swab), assay type, and date of test. **Efficacy Procedures:** <u>Nasal Swab and Saliva SARS-CoV-2 RT-qPCR Test (Central Lab)</u>: Nasal swab and saliva samples will be collected from subjects to determine presence or absence of SARS-CoV-2 virus and to explore relative quantitation of viral shedding.

COVID-19 Symptomology (Broad Terms and Strict Terms):

During each scheduled or unscheduled visit/contact, the investigator or sub-PI investigator, or designee (ie, nurse practitioner in countries where allowed by local law) will query the subject about adverse events the subject is experiencing or has experienced since the last visit/contact (eg, within the prior week if it's a weekly scheduled visit) and ask about all of the signs and symptoms associated with these adverse events including the start date, end date and severity of each. The investigator should avoid querying the subject by running a check-list of signs and symptoms, but rather allow the subject to spontaneously report everything that they presented.

All signs and symptoms related to the AEs, along with the corresponding start date, end date and severity should be documented in the subject's medical records (source document). As signs and symptoms may appear and resolve on different days and may precede or occur after the collection of nasal swab and saliva samples for the SARS-CoV-2 RT-qPCR test, it is important that this detailed information be captured in the source document.

Independent of the results (positive or negative) of the SARS-CoV-2 RT-qPCR tests performed on samples collected from study subjects during the weekly or unscheduled visits, all adverse events must be documented in the AE CRF. Signs and symptoms related to the adverse events reported in the AE CRF and confirmed to be temporally related to a positive SARS-CoV-2 RT-qPCR test collected from the subject's nasal swab and/or saliva sample will be reported on a separate CRF (individual sign or symptom with start date and end date, and associated severity).

Strict-term COVID-19 signs and symptoms, defined as:

- o fever (≥38°C) PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath);

  OR
- o 2 respiratory symptoms (sore throat, cough, shortness of breath);

  OR
- o 1 respiratory symptom (sore throat, cough, shortness of breath) PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise).

- Broad-term COVID-19 signs and symptoms: defined as any of the 23 symptoms (listed earlier in the Objectives) or fever (≥38°C).

Medically Attended Visits: Subjects who become SARS-CoV-2 RT-qPCR positive will be queried on any SARS-CoV-2 infection-related medically attended visits to the ED, UCC, or hospitalization starting from the timepoint of SARS-CoV-2 RT-qPCR positive and through the end of the EAP.

Absenteeism Assessment: Data include absenteeism, defined as number of days missed for daily responsibilities, including work (employed adults) or school (matriculating students), or family obligations/responsibilities (childcare or eldercare) due to COVID-19.

Safety Procedures:

Targeted Physical Examination and Vital Signs: The targeted physical examination and vital signs include measurements of temperature, blood pressure (measured after the subject has been resting quietly for at least 5

	minutes and may be obtained from a seated or supine position), pulse rate, and respiratory rate, and examination of the oropharynx, skin, heart, lungs and any other system(s) depending on any complaints or concerns expressed by the subjects. Laboratory Testing: samples for blood chemistry, hematology, and urinalysis will be collected and analyzed. For all women of childbearing potential, a urine pregnancy test will be performed onsite and any positive urine pregnancy test will be confirmed with a serum pregnancy test at the central laboratory. **Other Procedures:** Drug concentration and Immunogenicity measurements: Dense sample and sparse sample collection for drug concentration measurement will be performed in subsets of subjects. Any unused serum samples may be used for exploratory research. Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies: In order to assess the impact of baseline humoral immunity/antibody response to SARS-CoV-2 on REGN10933+REGN10987 efficacy to prevent SARS-CoV-2 infection, serum anti-SARS-CoV-2 will be measured at baseline, including but not limited to those which detect antibodies against the S protein and/or the N protein and/or neutralization assays. Exploratory Pharmacodynamic/Biomarker and Serum/Plasma Samples for Research: Samples for assessment of pharmacodynamic and exploratory research will be collected. Pharmacogenomic Analysis (Optional): Subjects may participate in an optional genomics sub-study (separate informed consent required). Blood sample for RNA and DNA will be collected for this substudy.
Statistical Plan	**Justification of Sample Size** ***Cohort A: SARS-CoV-2 RT-qPCR Negative*** In cohort A, subjects are randomized in a 1:1 allocation ratio to REGN10933+REGN10987 or placebo. There are 2 primary hypotheses: (1) the reduction in the proportion of symptomatic SARS-CoV-2 infections; and (2) the reduction in the proportion of symptomatic or asymptomatic SARS-CoV-2 infections. For the planning of sample size requiring to achieve at least 90% power, it is assumed that they will be tested in parallel at the 0.025 level. Note that both of these primary hypotheses are tested among those subjects who are seronegative at baseline. In this household design, both the number of subjects per household and the correlation between subjects in infection rates within household are both unknown. If there is only 1 subject per household, a sample size of 1368 seronegative subjects provide approximately 90% power to detect a relative risk of 0.5 (ie, 50% reduction of the assumed 10% placebo attack rate) considering an interim analysis when 50% of subjects complete EAP. Power was also calculated assuming that the same number of subjects derives from 640 households (yielding an average household size of 2.14 subjects) with varying degrees of correlation within household. In all cases, the power of the study is >90%. In order to obtain 1368 subjects in cohort A, approximately 1700 subjects will need to be enrolled, assuming that 10% of subjects drop out and 10% of subjects are seropositive at baseline. These power calculations also assume that the attack rate is 10% and 5% in placebo and REGN10933+REGN10987 groups, respectively, for both primary efficacy endpoints.

Since the number of subjects per household and the correlation among subjects within each household are both unknown, a sample re-estimation will be conducted by the IDMC after approximately 10% to 25% of subjects have completed the EAP.

Cohort B: SARS-CoV-2 RT-qPCR Positive

The key secondary endpoint in Cohort B is the reduction in the proportion of subjects who develop strict-term symptomatic SARS-CoV-2 infection.

The sample size of Cohort B assumes that approximately 15% of subjects in a household are already positive for SARS-CoV-2 by RT-qPCR at baseline. Therefore, among 2000 subjects enrolled in this study in order to obtain 1700 subjects for Cohort A, the number of subjects expected in Cohort B is approximately 300. Assuming that there would only be 1 subject per household and that 50% will develop symptoms, Cohort B will provide >95% power to detect a relative risk of 0.5 (ie, 50% risk reduction), using a 2-sided Fisher's exact test at alpha level of 0.05.

Control of Multiplicity

Cohort A: SARS-CoV-2 RT-qPCR Negative

The overall type I error will be controlled for primary hypotheses with a 2-sided test at an alpha level of 0.05 as follows:

> H1: No treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects who have a positive SARS-CoV-2 RT-qPCR (based on central lab testing) and signs and symptoms (strict term) of SARS-CoV-2 infection during the EAP.
>
> H2: No treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects have a RT-qPCR confirmed SARS-CoV-2 infection (either asymptomatic or symptomatic) during EAP.

When 50% of subjects complete the EAP, there will be an interim analysis. To control the overall type I error at alpha level of 0.05, the alpha will be spent using the Lan-DeMets alpha spending function that approximates the O'Brien-Fleming boundary. The Hochberg method will be applied for hypotheses H1 and H2 at a 2-sided alpha level of 0.05 when all subjects in Cohort A complete the EAP. If both p-values are ≤0.05, both H1 and H2 will be rejected and REGN10933+REGN10987 will be declared statistically significantly better than placebo. If 1 of the p-values is > 0.05, the other p-value will be compared with 0.025. If the smaller p-value is ≤0.025, the corresponding hypothesis will be rejected and the REGN10933+REGN10987 will be declared statistically significantly better than placebo.

If both primary efficacy endpoints are statistically significant, the alpha will be released for the key secondary endpoints.

Cohort B: SARS-CoV-2 RT-qPCR Positive

The overall type I error will be controlled at an alpha level of 0.05 for the formal hypothesis test as below.

> H1: No treatment difference between REGN10933+REGN10987 and placebo in proportion of subjects who subsequently develop signs and symptoms (strict term) of symptomatic SARS-CoV-2 within 14 days of a positive RT-qPCR

If the hypothesis is rejected, the full alpha will be used for the other key secondary endpoints. The details will be provided in SAP.

Full Analysis Set

Cohort A: SARS-CoV-2 RT-qPCR Negative

The full analysis set for Cohort A (FASA) includes all randomized subjects based on the treatment allocated (as randomized) who have laboratory confirmed negative tests for SARSCoV2 RT-qPCR and SARS-CoV-2 serology (both based on central lab testing). The primary efficacy endpoints and the secondary efficacy endpoints for cohort A will be analyzed using the FAS-A unless specified otherwise.

Cohort B: SARS-CoV-2 RT-qPCR Positive

The full analysis set for cohort B (FAS-B) includes all randomized subjects based on the treatment allocated (as randomized) who are laboratory confirmed positive at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing). The efficacy endpoints for cohort B will be analyzed using the FAS-B unless otherwise specified.

Primary Efficacy Analysis (Cohort A)

The primary efficacy endpoints will be analyzed in the FAS-A population. In order to account for the correlation among subjects within a household and control the associated type 1 error inflation, a generalized linear model will be used to estimate the odds ratio between the treatment groups by using the generalized estimation equation (GEE) approach. This model estimates a single within-household correlation coefficient.

If a subject's infection status cannot be determined due to all missing post-baseline serologic test results or RT-qPCR results during the efficacy assessment, that subject will be imputed as an event (ie, either symptomatic or asymptomatic positive SARS-CoV-2 RT-qPCR status). Additional missing data handling rules will be specified in the SAP. The model will at least include the fixed category effects of treatment group (placebo versus REGN10933+REGN10987) and randomization stratification factor age (<50, ≥50 years). The model will use a compound symmetry covariance matrix and estimate the odds ratio estimate between the treatment groups and corresponding 95% CI and p-value. If the generalized estimating equation model fails to converge due to most households containing only a single person then a logistic regression model will be used, with treatment and strata as fixed effects.

Safety Analysis

Safety and tolerability will be summarized by tabulation of treatment-emergent adverse events (TEAEs).

1. INTRODUCTION

1.1. Emergence of SARS-CoV-2 and COVID-19

Coronaviruses are a family of enveloped, single-stranded RNA viruses. In recent decades, two highly pathogenic strains of coronavirus were identified in humans: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses were found to cause severe, and sometimes fatal, respiratory illness (Cui, 2019) (Fehr, 2015).

In December 2019, a pneumonia of unknown cause was identified in clusters of patients in Wuhan City, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the viral infection was later designated coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO, 2020b) (Zhu, 2020). As of June 2020, more than 7.6 million confirmed cases of COVID-19 have been reported globally (WHO, 2020a). This rapidly-spreading, worldwide outbreak prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern on 11 March 2020.

1.2. Populations at Increased Risk of SARS-CoV-2 Infection Among Household Contacts of a Person Infected with SARS-CoV-2

Efforts to control the pandemic have resulted in widespread shelter-in-place orders. Transmission of SARS-CoV-2 occurs primarily through person-to-person contact and respiratory droplet transmission (Lai, 2020). Household contacts of a person infected with SARS-CoV-2 are at a high risk for acquiring infection, with transmission rates ranging from approximately 10% to 15%. The majority of individuals who acquire infection from household contacts develop symptoms of COVID-19 (Burke, 2020) (Jing, 2020), (Bi, 2020) (Li, 2020b). Prophylaxis is urgently needed to reduce transmission rates and/or reduce the occurrence of symptomatic disease. Ideally, prophylaxis would need to be given as soon as possible after a known exposure, as the duration of time between symptomatic infection in the source individual and the development of symptoms in newly infected individual is thought to be approximately 5 days, with a possible range of 2 to14 days (Lauer, 2020) (Li, 2020a). Animal models suggest that SARS-CoV-2 RT-PCR in nasopharyngeal (NP) samples become positive within a few days after infection (Rockx, 2020). An ideal agent for prophylaxis should be fast acting and highly effective and should protect against multiple viral variants. A monoclonal antibody (mAb) combination therapy, with two different monoclonal antibodies that bind distinct regions of the portion of the SARS-CoV-2 spike (S) protein that bind to and facilitate entry into host cells, has been developed in order to achieve these goals. A mAb combination against SARS-CoV-2 for post-exposure prophylaxis that can either prevent the development of disease or reduce viral acquisition or shedding could be key to reducing transmission of the virus and limiting symptoms and adverse outcomes following infection.

1.3. The Role of Spike Protein in SARS-CoV-2 Pathogenesis

Coronaviruses consist of an RNA genome packaged in nucleocapsid (N) protein surrounded by an outer envelope. The envelope is comprised of membrane (M) protein and envelope (E) protein, which are involved in virus assembly, and spike (S) protein, which mediates entry into host cells. S proteins form large trimeric projections, providing the hallmark crown-like appearance of coronaviruses. S protein trimers bind to a host receptor and, after priming by cellular proteases, mediate host–virus membrane fusion (Li, 2016). The S protein appears to be central to viral infectivity by SARS-CoV-2. SARS-CoV-2 S protein binds the host receptor angiotensin-converting enzyme 2 (ACE2) with high affinity, and in cell assays and animal models can utilize ACE2 as a functional receptor for host cell entry (Ou, 2020) (Hoffmann, 2020) (Walls, 2020).

Blockade of host cell entry through the use of neutralizing antibodies against S protein is a viable mechanistic strategy shown to reduce viral infectivity of SARS-CoV and MERS-CoV (Jiang, 2020). In light of the likely pivotal role of spike protein in the pathogenesis of SARS-CoV-2, a number of efforts are underway to develop antibodies and vaccines that target the S protein of this novel coronavirus.

1.4. REGN10933+REGN10987: Fully Human Monoclonal Antibodies that Target SARS-CoV-2 S Protein

Regeneron Pharmaceuticals, Inc (Regeneron) is currently developing fully human, neutralizing mAbs directed against the S protein of SARS-CoV-2, for the treatment and prevention of SARS-CoV-2 infection. REGN10933 and REGN10987 are fully human, IgG1 mAbs that bind to distinct regions of the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2. REGN10933 and REGN10987 exhibit potent neutralization and can bind simultaneously to the S protein RBD. When co-administered as combination therapy, REGN10933+REGN10987 prophylaxis is anticipated to neutralize SARS-CoV-2 with a reduced likelihood of viral escape due to genetic mutations. In vitro experiments designed to specifically test for viral escape under selective pressure have shown that the combination of REGN10933+REGN10987 was resistant to escape while some single anti-Spike protein monoclonal antibodies were vulnerable to escape. REGN10933+REGN10987 combination therapy thus represents a promising prophylaxis strategy to reduce SARS-CoV-2 infection upon exposure to SARS-CoV-2.

1.5. A Randomized, Placebo-Controlled Study of Anti- Spike Protein Monoclonal Antibodies as Post-Exposure Prophylaxis and Pre-emptive Therapy in Household Contacts

Many therapeutic agents have been studied in the context of other coronaviruses (SARS-CoV and MERS-CoV), including corticosteroids, type 1 interferons, convalescent plasma, ribavirin, lopinavir/ritonavir, proteases, and agents targeting viral entry proteins, with generally inconsistent findings of efficacy (Sanders, 2020). Several of these therapies, as well as a number of other potential treatments and vaccines, are currently under investigation for the treatment of SARS-CoV-2. On 1 May 2020, remdesivir received Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) for the treatment of hospitalized patients with COVID-19 (FDA, 2020). Currently, however, there is no approved prophylaxis for COVID-19 nor for patients that are infected with SARS-CoV-2 but are asymptomatic. Given the speed at which this outbreak has spread and how it has impacted almost every community globally, there is an urgent need to develop safe and efficacious interventions to slow the spread of the SARS-CoV-2 virus and decrease adverse outcomes associated with symptomatic disease.

This is a pivotal phase 3 randomized, double-blind, placebo-controlled study in adults with household contact exposure to individuals with SARS-CoV-2 infection in geographic areas with an active COVID-19 outbreak. This study is designed to assess the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") to reduce the proportion of SARS-CoV-2 infections and prevent the development of COVID-19 disease (symptomatic SARS-CoV2 infection), after household exposure to individuals with SARS-CoV-2 infection. Safety, tolerability, pharmacokinetics (PK), and immunogenicity of REGN10933+REGN10987 will also be evaluated.

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2. Additional background information on the study drugs and the overall development program can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

All subjects in the study will be household contacts of a SARS-CoV-2 infected individual but who are themselves asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening.

For analysis of endpoints, there are 2 defined cohorts based on the subjects' SARS-CoV-2 infection status at baseline, as measured by central lab SARS-CoV-2 RT-qPCR (quantitative reverse transcription polymerase chain reaction): negative (cohort A) or positive (cohort B).

Results of the local molecular diagnostic assay for SARS-CoV-2 from respiratory samples and on-site serology tests at baseline will be used as stratification factors for randomization and treatment group allocation, but not for the designation of cohorts for data analysis.

Cohorts are described Section 3.2.3 and are defined in Section 6.1.5. Study objectives and endpoints are specified for each cohort (Section 2 and Section 4).

The definition for "strict-term" and "broad-term" signs/symptoms of SARS-CoV-2 infection is presented in Section 9.2.2.2.

Objectives are for subjects who are seronegative at baseline (based on central lab test) unless noted.

2.1. Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline

2.1.1. Cohort A Primary Efficacy Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (strict-term) confirmed by RT-qPCR
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR

2.1.2. Cohort A Primary Safety Objective

- To evaluate the safety and tolerability of REGN10933+REGN10987 following subcutaneous (SC) administration compared to placebo

2.1.3. Cohort A Secondary Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR test results

- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration in seropositive subjects
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects

2.1.4. Cohort A Exploratory Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing SARS-CoV-2 infection assessed by seroconversion in baseline seronegative subjects
- To explore the impact of REGN10987+REGN10933 compared to placebo:
  - On humoral immune response to SARS-CoV-2 infection
  - On measures of infectivity of SARS-CoV-2 as assessed in experimental laboratory assays
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 re-infection in subjects who are seropositive at baseline:
  - Prevention of symptomatic re-infection (strict-term)
  - Prevention of symptomatic re-infection (broad-term)
  - Prevention of symptomatic re-infection (strict-term or broad-term) or asymptomatic infection
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR test results in subjects who are seropositive at baseline
- To explore the relationships between REGN10933+REGN10987 exposure and selected clinical efficacy and safety endpoints and/or biomarkers in seropositive and seronegative subjects
- To assess viral genetic variation in SARS-CoV-2 in subjects with a positive SARS-CoV-2 RT-qPCR
- To explore biomarkers (including host genome variants) associated with safety and efficacy of REGN10933+REGN10987 and to study SARS-CoV-2

2.2. Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline

2.2.1. Cohort B Secondary Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing development of:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR test results
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration in both seronegative and seropositive subjects
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects

2.2.2. Cohort B Exploratory Objectives

- To explore the impact of REGN10987+REGN10933 compared to placebo on SARS-CoV-2 infection:
  - On humoral immune response
  - On measures of infectivity of SARS-CoV-2 as assessed in experimental laboratory assays
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in subjects who are seropositive at baseline in preventing:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term)

- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR test results in subjects who are seropositive at baseline
- To explore the relationships between REGN10933+REGN10987 exposure and selected clinical efficacy and safety endpoints and/or biomarkers in seropositive and seronegative subjects
- To assess viral genetic variation in SARS-CoV-2 in subjects with a positive SARS-CoV-2 RT-PCR.
- To explore biomarkers (including host genome variants) associated with safety and efficacy of REGN10933+REGN10987 and to study SARS-CoV-2

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline

Prophylaxis with SC administration of anti-spike REGN10933+REGN10987 will:

1. Prevent the occurrence of symptomatic infection with SARS-CoV-2.
2. Prevent the occurrence of asymptomatic and symptomatic infection with SARS-CoV-2.
3. Be well-tolerated.

Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline

Preemptive therapy with SC administration of REGN10933+REGN10987 will:

1. Prevent the development of symptomatic SARS-CoV-2 infection in household contacts who already have a positive SARS-CoV-2 RT-qPCR test at baseline
2. Be well-tolerated.

3.2. Rationale

3.2.1. Study Design

This randomized, double-blind, placebo-controlled, phase 3 study will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 in adults who are household contacts of a person infected with SARS-CoV-2. Collection of clinical and virologic data using a standardized timeline will provide valuable information on the clinical course of SARS-CoV-2 infection and the impact of these mAbs to prevent infection and symptomatic disease associated with SARS-CoV-2. The multicenter conduct of this study will enable generalizable evidence of the safety, tolerability, and efficacy of investigational mAbs. Specifically, this study is intended to demonstrate the efficacy of REGN10933+REGN10987 to prevent SARS-CoV-2 infection (with or without symptoms) in uninfected subjects or prevent symptomatic disease (eg, preemptive therapy) in subjects already infected (ie, SARS-CoV-2 RT-qPCR positive) at baseline. The double-blind design serves to reduce potential bias introduced by knowing the study drug assignment. The comparator arm in this study will be placebo as no approved preventative treatments are currently available. The placebo arm will also provide an estimate of the background incidence of SARS-CoV-2 infection and disease, as well as of adverse event (AE) rates for both efficacy and safety analyses. Additionally, all subjects' SARS-CoV-2 serology status, including baseline, will also remain blinded during the study to avoid potential bias introduced by the study site personnel when evaluating and assessing subjects who are seropositive and to mitigate the possibility of less risk averse behaviors in which subjects might engage. The study size and duration were driven by current epidemiological assumptions about study population and are detailed in Section 11.2.

This study will be preceded by safety review of data from other studies: a safety sentinel group of 30 patients with COVID-19 dosed with REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 8000 mg IV or placebo in the leading phase 1 studies of REGN10933+REGN10987 in the treatment of COVID-19 patients. Randomization in this study will not begin until the Independent Data Monitoring Committee (IDMC) for the treatment studies provides a "study may proceed" conclusion from the IV dosing sentinel group (Section 3.2.4).

All subjects in the study will be household contacts of a SARS-CoV-2 infected individual but who are themselves ***asymptomatic*** (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening. Randomization will be performed on an individual subject basis rather than by household, however all subjects randomized will be given a household identification number in the case that multiple members of the same household are enrolled and receive study drug. This ensures that correlation among subjects within the same household may be considered in the statistical analysis.

The study will consist of a screening/baseline period that will occur on the same day, due to the short window (96 hours) between the collection of the index cases' positive SARS-COV-2 RT-PCR sample and randomization of the study subject(s). This same day screening/baseline period is expected to decrease the burden of study visits on the subject and might help to increase subject engagement. For the same reason, only a subset of subjects (by subject ordinal number as first subjects are randomized using the interactive web response system [IWRS]) will undergo PK and intensive safety laboratory testing throughout the study (approximately 30 subjects for dense PK sampling, approximately 400 subjects for sparse PK sampling, and intensive safety laboratory assessments). The number of subjects selected for PK sampling and for intensive safety lab assessments are considered sufficient to provide an adequate evaluation of the different parameters.

At the screening/baseline visit, subjects will have a local, molecular diagnostic assay for SARS-CoV-2 from respiratory samples and an on-site serology test. The results of these local tests will be used as stratification factors for randomization for assigning subjects into 1 of 2 treatment groups. In the event that local testing results are not available in the time required during screening, subjects may be randomized. Subjects will also have samples collected at baseline for central lab SARS-CoV-2 RT-qPCR tests. The results of the central lab RT-qPCR (the results of which may not be available on the same day due to time for shipping) will be used for cohort allocation into cohort A (negative) or cohort B (positive) for data analysis.

The first 30 subjects enrolled in the REGN10933+REGN10987 prophylaxis program will complete day 4 safety assessments from either this study or pooled with an accompanying pre-exposure prophylaxis study in at risk subjects (R10933-10987-COV-2068) which comprise a sentinel safety cohort. Subjects will be monitored at the study site for 4 hours after the single-dose

SC study drug administration and including being specifically monitored for acute hypersensitivity reactions or injection site reactions, which constitute the primary potential risks with SC injection of a fully human monoclonal antibody against an exogenous target. Subjects will be assessed daily for the first 4 days after study drug administration for evaluation of treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESI). Blinded safety data will be reviewed before progressing with enrollment of additional study subjects. This close observation of the first 30 subjects is considered sufficient to assess safety and allow further enrollment of study subjects as the risk for AEs or AESIs is highest during the first days following study drug administration. This sentinel safety monitoring is considered adequate because REGN10933+REGN10987 will already have cleared a sentinel safety group at higher doses (2400 mg and 8000 mg) administered IV.

The study has a 28-day efficacy assessment period (EAP) after the single dose of active study drug or placebo administered SC to capture all infections as detected by SARS-CoV-2 RT-qPCR positivity (both asymptomatic and symptomatic), symptomatic infection (ie, those individuals that experience symptoms consistent with SARS-CoV-2 infection and progression of COVID-19 disease). A 28-day assessment period is expected to be sufficient to accrue an adequate number of primary endpoint events within the planned sample size. The incubation period of SARS-CoV-2 after exposure is approximately 2 to 14 days (Li, 2020a) (Lauer, 2020). The duration of mild to moderate symptoms, including time to hospitalization, is approximately 11.5±5.7 days (Lechien, 2020). Following the 28-day EAP, subjects will undergo a 7-month follow-up period to assess for TEAEs, PK, and anti-drug antibodies (ADA). This duration is based on a half-life of 21-days for a typical mAb. This follow-up period is expected to allow an assessment of safety after discontinuing treatment. The length of the follow-up period may be modified based on the observed PK and ongoing nonclinical data as it becomes available. The occurrence and severity of any suspected COVID-19 related AEs (including SAEs) that occur as drug concentrations wane will be monitored, and subjects who received active drug or placebo will be assessed for any signal of ADE.

3.2.2. Subject Population

The study population will consist of approximately 2000 adults with household contact exposure to individuals with a confirmed SARS-CoV-2 infection. In this study, the household contact must share the same residential address and have a sustained close exposure with an individual with SARS-CoV-2 infection (index case). To be included in the study, subjects must be randomized within 96 hours of collection of the index cases' positive SARS-COV-2 RT-PCR sample. Household contacts of individuals infected with SARS-CoV-2 are at a high risk for acquiring infection, with transmission rates ranging from approximately 10% to 15% in these settings (Burke, 2020) (Jing, 2020) (Li, 2020b). Therefore, approximately 15% of subjects are expected to develop symptomatic disease in follow up after a household contact transmission event (Li, 2020b). A minority of subjects are expected to be seropositive at baseline, as seropositivity in the general population, outside of hard-hit areas like New York City, is expected to be less than 10% (Burke, 2020). Subjects with positive rapid SARS-CoV-2 RT-PCR at the time of randomization, who are either seronegative or seropositive at baseline will also be included in the study, but only subjects who are both seronegative and negative for SARS-CoV-2 infection by rapid RT-PCR at randomization at baseline will be included in the primary efficacy analysis.

3.2.3. Enrollment by Baseline SARS-CoV-2 Infection Status and Stratification by Baseline Serology

This study will include asymptomatic subjects regardless of baseline SARS-CoV-2 infection status or serologic status. Including all-comers into the study will provide important information on infection prevention through prophylaxis as well as the impact of pre-emptive therapy in infected but asymptomatic individuals. Since the primary efficacy objectives are focused on the prevention of asymptomatic or symptomatic SARS-CoV-2 infection, the primary population of interest are subjects that are seronegative and SARS-CoV-2 RT-PCR negative at baseline. It is estimated that approximately 10% of the study population will be seropositive at baseline. Therefore, the majority of subjects enrolled are expected to be allocated to the primary study population of interest, seronegative and SARS-CoV-2 RT-PCR negative at baseline (ie, cohort A).

On day 1 and prior to randomization, subjects will have a local molecular diagnostic assay for SARS-CoV2 from a respiratory sample and an on-site serology test (lateral flow immunoassay [LFIA] test), as well as samples collected for central lab SARS-CoV-2 RT-qPCR and serology tests. The results of the local lab tests will be available the same day and will be used as stratification for randomization to allow administration of study drug. In the event that local testing results are not available in the time required during screening, subjects may be randomized.

For data analysis, subjects will be divided into 2 independent study cohorts: cohort A or cohort B. This allocation will be based on a central lab SARS-CoV-2 RT-qPCR test result performed during the screening/baseline visit. While stratification and randomization will be based on local test results, data analyses will be based on the central lab results of baseline SARS-CoV-2 RT-qPCR results from nasal and saliva samples and the serological status.

The analysis of the subject populations that are not part of the primary study population of interest (ie, those subjects in cohort A who are seropositive at baseline) and all subjects in cohort B (ie, subjects who are SARS-CoV-2 RT-qPCR positive at baseline, irrespective of the serology status being positive or negative) will not contribute to a primary study objective or endpoint. These individuals will be analyzed separately either through secondary or exploratory objectives and endpoints.

To mitigate enrollment of a high percentage of subjects that are either seropositive or SARS-CoV--2 RT-qPCR positive at baseline, those with a known prior history of a positive SARS-CoV-2 RT-PCR test, a positive serology test, or COVID-19 will be excluded.

All subjects' SARS-CoV-2 qualitative diagnostic test results will be unblinded during the study. This will ensure SARS-CoV-2 infected individuals take the appropriate precautions necessary to prevent spread of disease. However, all subjects' SARS-CoV-2 serology post-baseline results will remain blinded during the study to avoid potential bias introduced by the study site personnel when evaluating and assessing subjects who are seropositive and to avoid encouraging higher risk behaviors through disclosure of seropositivity.

3.2.4. Sentinel Safety Group and Subsequent Safety Reviews

Driven by the medical urgency of the COVID-19 pandemic, the process described below is designed to maximize efficient enrollment of eligible subjects while optimizing the safety of the first SC administration of REGN10933+REGN10987. Clinical safety and tolerability data from the pooled sentinel cohorts from treatment studies (R10933-10987-COV-2066 and

R10933-10987-COV-2067) in COVID-19 patients receiving IV administration of REGN10933+REGN10987 is expected prior to first SC dosing in this study.

The description of the sentinel group, safety monitoring of sentinel subjects, and data review is provided in Section 6.1.1. Regular safety data review and evaluation by IDMC is described in Section 6.3.1.

3.2.5. Primary Objectives

The primary objectives of this study are to evaluate the safety and efficacy of REGN10933+REGN10987 in asymptomatic adults at risk for SARS-CoV-2 infection that are SARS-CoV-2 qRT-PCR negative and seronegative at baseline.

The FDA Guidance on COVID-19 recommends that in prevention trials, the primary endpoint should be the occurrence of laboratory-confirmed SARS-CoV-2 infection, with or without symptoms. Consistent with that guidance, the evaluation of efficacy in this phase 3 study will be based on both a virologic and a clinical endpoint.

Virologic efficacy: The primary mechanism of action of REGN10933+REGN10987 is blockade of the S protein RBD interaction with ACE2, leading to inhibition of SARS-CoV-2 host cell infection. The ability of REGN10933+REGN10987 treatment to prevent SARS-CoV-2 infection will be evaluated by SARS-CoV-2 RT-qPCR test results from weekly nasal swabs and saliva samples. Weekly sample collection is considered an adequate collection frequency to ensure early detection of viral shedding in infected individuals; this is based the average duration of viral positivity from NP swabs ranges from 7 to 28 days (He, 2020) (Wolfel, 2020). All subjects will have SARS-CoV-2 RT-qPCR testing by nasal and saliva samples. Nasal swab testing has been shown to have good sensitivity and specificity for detecting SARS-CoV-2 RNA (Zou, 2020) (Pere, 2020) and is better tolerated than NP swab testing. More recently, RT-qPCR from saliva samples has been shown in a few studies to have increased sensitivity when compared to NP samples (Wyllie, 2020).

Clinical efficacy: The ability of REGN10933+REGN10987 administration to prevent symptomatic SARS-CoV-2 infection will be evaluated through weekly inquiry by the investigator to assess if subjects experienced or are experiencing commonly reported clinical signs/symptoms related to COVID-19. A strict definition of signs/symptoms associated with COVID-19 (see Section 9.2.2.2 for full definition) will be utilized for the primary endpoint rather than a broader definition including non-specific symptoms. There is concern that a broader definition of the syndromic COVID-19 diagnosis may inflate reporting, underestimate treatment effects, decrease specificity and negatively impact the reliability of the symptomatic endpoint, especially in the context of an individual becoming aware of their SARS-CoV-2 RT-qPCR positivity. The clinical signs/symptoms of the strict definition of SARS-CoV-2 infection include: fever, respiratory symptoms (sore throat, cough, shortness of breath), and non-respiratory symptoms (chills, nausea, vomiting, diarrhea, conjunctivitis, headache, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise) (see details in Section 9.2.2.2).

In addition to the primary objectives, the secondary objectives will assess other important clinical outcome measures including a broader definition of symptomology associated with SARS-CoV-2 infection, healthcare utilization (seeking an emergency room or urgent care facility, hospitalization, length of hospital stay, etc), and the duration of disease in subjects who develop symptomatic infection. Similar objectives will be applied to subjects who are SARS-CoV-2 RT-PCR positive and/or seropositive at baseline.

3.2.6. Rationale for Dose Selection

This study will assess a single SC dose of REGN10933+REGN10987 as combination therapy in a 1:1 ratio. The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are noncompeting mAbs targeting non-overlapping epitopes of the RBD of the S protein of SARS-CoV-2, with similar in vitro binding and neutralization properties (for more information, refer to the Investigator's Brochure). The study will evaluate REGN10933+REGN10987 as combination therapy at a 1200 mg (600 mg of each mAb) SC dose.

Angiotensin converting enzyme subtype 2 expression has been reported in the lungs, particularly in type-2 alveolar epithelial cells and bronchial airway epithelium (Wu, 2020) (Xu, 2020) (Zhao, 2020). The strategy taken for dose selection in this study was to identify a target concentration in lung epithelial lining fluid (ELF) that approximates the effective concentration required for 99% neutralization (EC_{99}) of SARS-CoV-2 in vitro and to then identify a dose that will meet or exceed this concentration in lung ELF. The EC_{99} against SARS-CoV-2 in vitro is 0.14 µg/mL for REGN10933 and 0.80 µg/mL for REGN10987.

An average lung ELF-to-serum mean C_{max} ratio of ~0.15 has been reported for other exogenous IgG1 mAbs for the treatment of Staphylococcus aureus lung infections (Magyarics, 2019). It is assumed that the lung ELF-to-serum C_{max} ratio is 0.15 for REGN10933 and REGN10987. Dividing the target lung ELF concentration by this ratio, the associated serum concentration for these targets is therefore estimated to be ~at least 5 µg/mL for the combination of REGN10987+REGN10933.

Taking into account uncertainties regarding mAb penetration into lung ELF, prediction of human PK, and effects of disease on PK, 20 µg/mL was selected as a target concentration in serum for the 600 mg SC per mAb REGN10933+REGN10987 combination dose. The goal for this REGN10933+REGN10987 combination dose is for ≥95% of subjects to exceed the target serum concentration for 28 days after dosing. To estimate the clinical SC dose required to achieve this goal, a population PK model developed for a typical Regeneron mAb administered SC was used to simulate mean and 5th percentile serum concentrations for a virtual population of 2,000 subjects (mean (SD) [min, max] body weight of 85 (17) [40, 150] kg) for various SC doses.

For a single 600 mg per mAb SC dose, ≥95% of subjects are predicted to exceed the target serum concentration by approximately 1 day after the first dose and remain above the target serum concentration for the remainder of the 28-day treatment period, for each mAb.

A 4-week GLP toxicology study in cynomolgus monkeys is currently ongoing and assessing once weekly dosing of up to 150/150 mg/kg per mAb administered once weekly (for combination) to support safety of the anti-SARS-CoV-2 spike mAbs (for more information, refer to the Investigator's Brochure).

3.3. Risk-Benefit

This study represents 1 of 2 initial prophylaxis studies planned to evaluate REGN10933+REGN10987 as a SC injection in humans. Therefore, the potential clinical benefits and risks associated with the study drugs are yet to be determined. Several preclinical pharmacokinetic, pharmacologic, and toxicology studies are ongoing and/or planned, and findings from these studies will be appropriately communicated. While initial preclinical data are available (discussed below), the anticipated risks are based primarily on prior Sponsor experience with similar fully human monoclonal antibody development programs against exogenous targets and the potential risks associated with subcutaneous injection of fully human monoclonal antibodies in general.

A 4-week GLP toxicology study in cynomolgus monkeys is currently ongoing and assessing once-weekly intravenous and SC dosing of REGN10933+REGN10987 at up to 150 mg/kg per antibody. Initial findings from an interim 1-week data cut of the toxicology study identified no clinically relevant risks or test article-related adverse effects. Separately, preliminary findings from a tissue cross reactivity study was notable for by the absence of any tissue cross reactivity with either REGN10933 or REGN10987 in any of the human or monkey tissues evaluated. Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy on the fetus and reproductive organs in males and females are unknown.

REGN10933 and REGN10987 target the SARS-CoV-2 S protein, an exogenous protein. The Sponsor has significant experience with prior development programs for fully human mAbs against exogenous targets, including atoltivimab, odesivimab, and maftivimab (Ebola), REGN3048 and REGN3051 (MERS-CoV), REGN5713, REGN5714 and REGN5715 (Bet v 1 birch tree allergen), and REGN1908 and REGN1909 (Fel d 1 cat dander allergen). No significant safety findings were observed in any of the associated toxicology studies conducted and the mAbs demonstrated an acceptable safety profile in the clinical studies.

The important potential risks are thus limited to those typically associated with a mAb administered by SC route: injection site reactions, hypersensitivity reactions, and immunogenicity. REGN10933 and REGN10987 are fully human IgG1 mAbs, and correspondingly the risk of injection site reactions, hypersensitivity reactions, or immunogenicity is expected to be low. However, given the limited experience with these mAbs and the evolving understanding of SARS-Cov-2 infections, all TEAEs will be collected during the study to adequately characterize the safety profile of REGN10933+REGN10987.

Antibody-dependent enhancement (ADE) has also been observed for some therapeutics targeting exogenous viral proteins. For antibody therapies, ADE is thought to occur when binding of antibody to the target viral protein enhances FcγR-mediated host cell entry of the virus (Iwasaki, 2020). This could potentially lead to worsening of disease and, in the case of SARS, acute lung injury (Liu, 2019). REGN10933 and REGN10987 retain the Fc region, as this may play a role in protecting against viral infection (Yasui, 2014). However, there is no strong evidence of ADE in other coronavirus models (Kam, 2007) (Liu, 2019) (Luo, 2018) (Wang, 2016) (Weingartl, 2004). To date, Fc-containing mAbs developed by the Sponsor for Ebola virus, and MERS-CoV have demonstrated specificity to their exogenous targets with no significant unexpected safety findings in preclinical or clinical studies. All subjects will be monitored for TEAEs during the drug elimination period.

With respect to efficacy, the currently available in vitro data (Section 3.2.7 and the Investigator's Brochure) show that REGN10933+REGN10987 is anticipated to be pharmacologically active at the planned dose, with expected neutralization and effector functions against the SARS-CoV-2 S protein. Additionally, the only control measures that are currently available against this virus is practicing rigorous infection control. There is no therapeutic option for the prevention of

SARS-CoV-2 infection and there is an urgent need for a preventative treatment given the wide-reaching, devastating effects of this global outbreak.

In summary, based on prior experience with other fully human mAbs against exogenous targets, the available nonclinical data for REGN10933+REGN1098 to date, and the unmet need for a preventative therapy in advance of an approved vaccine, it is the opinion of the Sponsor that the overall risk-benefit balance for REGN10933+REGN10987 is acceptable to allow evaluation of this mAb combination in this adult population of household contacts of an infected individual and therefore at high risk for SARS-CoV-2 infection.

For more details, refer to the Investigator's Brochure.

4. ENDPOINTS

Endpoints are specified for study cohorts (as defined in Section 6.1.5).

Symptomatic SARS-CoV-2 infection is determined by a positive central lab SARS-CoV-2 RT-qPCR result during the EAP with signs/symptoms occurring within ±14 days of a positive RT-qPCR.

The definition for "strict-term" and "broad-term" signs/symptoms of SARS-CoV-2 infection is presented in Section 9.2.2.2.

The endpoints are for subjects who are seronegative at baseline (based on central lab test), unless otherwise noted.

4.1. Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline

4.1.1. Cohort A Primary Endpoints

Primary Efficacy Endpoint

- Proportion of subjects who have a positive SARS-CoV-2 RT-qPCR (based on central lab test) and signs and symptoms (strict-term) of SARS-CoV-2 infection during the EAP
- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (either asymptomatic or symptomatic) during the EAP

Primary Safety Endpoints

- Proportion of subjects with TEAEs and severity of TEAEs

4.1.2. Cohort A Secondary Endpoints

Cohort A Secondary Efficacy Endpoints

- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
- Proportion of subjects who have a positive SARS-CoV-2 RT-qPCR and the absence of signs and symptoms (strict-term) during the EAP

- Proportion of subjects who have a positive SARS-CoV-2 RT-qPCR and the absence of signs and symptoms (broad-term) during the EAP
- Number of days of symptomatic SARS-CoV-2 infection (strict-term) from the first day of the first sign or symptom until the last day of the last sign or symptom associated with the first positive SARS-CoV-2 RT-PCR that occurs during the EAP
- Number of days of symptomatic SARS-CoV-2 infection (broad-term) from the first day of the first sign or symptom until the last day of the last sign or symptom associated with the first positive SARS-CoV-2 RT-PCR that occurs during the EAP
- Time-weighted average of viral shedding (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR nasal swab sample (that has an onset during the EAP) until 22 days after the positive test during the EAP
- Time-weighted average of viral shedding (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR saliva sample (that has an onset during the EAP) until 22 days after the positive test during the EAP
- Maximum SARS-CoV-2 RT-qPCR log10 viral copies/mL in nasal swab samples among individuals with ≥1 RT-qPCR positive that has an onset during the EAP
- Maximum SARS-CoV-2 RT-qPCR log10 viral copies/mL (saliva samples) among individuals with ≥1 RT-qPCR positive that has an onset during the EAP
- Area under the curve (AUC) in viral shedding (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR nasal swab sample until the first confirmed negative test, that has an onset during the EAP
- Area under the curve (AUC) in viral shedding (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR saliva swab sample until the first confirmed negative test, that has an onset during the EAP
- Number of medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Number of days missed for daily responsibilities, including work (employed adults) or school (matriculating students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP

Cohort A Safety Endpoints

- Proportion of baseline seropositive subjects (based on central lab test) with TEAEs and severity of TEAEs
- Incidence and severity of symptomatic SARS-CoV-2 infection in seronegative and seropositive subjects (based on central lab test) in both the EAP and follow up period

Cohort A Pharmacokinetic and Immunogenicity Endpoints

- Concentrations of REGN10933+REGN10987 in serum over time and selected PK parameters in both seronegative and seropositive subjects (based on central lab test)
- Immunogenicity as measured by anti-drug antibodies (ADAs) to REGN10933+REGN10987 over time in both seronegative and seropositive subjects (based on central lab test)

4.1.3. Cohort A Exploratory Endpoints

The exploratory endpoints for Cohort A are:

- Proportion of baseline seronegative subjects who become seropositive (based on central lab test) up to day 57
- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP
- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad term) SARS-CoV-2 infection during the EAP
- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR during the EAP
- Time-weighted average of viral shedding (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in nasal swab sample (that has an onset during the EAP) until 22 days after the positive test in seropositive subjects (based on central lab test) during the EAP
- Time-weighted average of viral shedding (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR saliva sample (that has an onset during the EAP) until 22 days after the positive test in seropositive subjects (based on central lab test) during the EAP
- Area under the curve (AUC) in viral shedding (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR nasal swab sample until the first confirmed negative test, in seropositive subjects (based on central lab test) that has an onset during the EAP
- Area under the curve (AUC) in viral shedding (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR nasal swab sample until the first confirmed negative test, in seropositive subjects (based on central lab test) that has an onset during the EAP

4.2. Cohort B

4.2.1. Cohort B Secondary Endpoints

- Proportion of subjects who subsequently develop signs and symptoms (strict-term) of symptomatic SARS-CoV-2 during the EAP within 14 and 28 days of a positive RT-qPCR
- Proportion of subjects who subsequently develop signs and symptoms (broad-term) of symptomatic SARS-CoV-2 infection during the EAP within 14 and 28 days of a positive RT-qPCR
- Number of days of symptomatic SARS-CoV-2 infection (strict-term)
- Number of days of symptomatic SARS-CoV-2 infection (broad-term)
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) in nasal swab samples until day 23
- Time-weighted average change from baseline in viral shedding (log_{10} copies/mL) in saliva samples until day 23
- Area under the curve (AUC) in viral shedding (log_{10} copies/mL) in nasal swab samples until the first confirmed negative test
- Area under the curve (AUC) in viral shedding (log10 copies/mL) in saliva swab samples until the first confirmed negative test
- Maximum SARS-CoV-2 RT-qPCR log_{10} viral copies/mL in nasal swab samples
- Maximum SARS-CoV-2 RT-qPCR log_{10} viral copies/mL in saliva samples
- Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection
- Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection
- Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection
- Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection
- Number of days missed for daily responsibilities, including work (employed adults) or school (matriculating students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection

Cohort B Safety Endpoints

- Proportion of subjects with TEAEs and severity of TEAEs in both seronegative and seropositive subjects (based on central lab test)
- Incidence and severity of symptomatic SARS-CoV-2 infection in seronegative and seropositive subjects (based on central lab test) in both the EAP and follow up period

Cohort B Pharmacokinetic and Immunogenicity Endpoints

- Concentrations of REGN10933 and REGN10987 in serum over time and selected PK parameters in both seronegative and seropositive subjects (based on central lab test)
- Immunogenicity as measured by anti-drug antibodies (ADA) to REGN10933 and REGN10987 over time in both seronegative and seropositive subjects (based on central lab test)

4.2.2. Cohort B Exploratory Endpoints

- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have symptomatic (strict-term) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP
- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have symptomatic (broad-term) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP
- Time-weighted average change and percent change from baseline viral shedding ($\log_{10}$ copies/mL) by SARS-CoV-2 RT-qPCR in nasal swab samples until day 23 in seropositive subjects (based on central lab test)
- Time-weighted average change and percent change from baseline in viral shedding ($\log_{10}$ copies/mL) by SARS-CoV-2 RT-qPCR in saliva samples until day 23 in seropositive subjects (based on central lab test)
- Area under the curve (AUC) in viral shedding ($\log_{10}$ copies/mL) in nasal swab samples until the first confirmed negative test, in seropositive subjects (based on central lab test)
- Area under the curve (AUC) in viral shedding ($\log_{10}$ copies/mL) in saliva swab samples until the first confirmed negative test, in seropositive subjects (based on central lab test)

5. STUDY VARIABLES

This section provides variables to be measured in the study. For description and rationale of corresponding study procedures, refer to Section 9.2.

5.1. Demographic and Baseline Characteristics

The variables for baseline characteristics include standard demography (eg, age, race, weight, height, body mass index [BMI], risk factors for SARS-CoV-2 infection, etc), medical history, medication history, and local molecular diagnostic assay for SARS-CoV-2 RT-PCR from respiratory samples and serology (anti-SARS-CoV-2 IgG/IgM; LFIA) test results, and central lab SARS-CoV-2 RT-qPCR and serology (anti-SARS-CoV-2 antibodies) test results for each subject.

5.2. Efficacy Variables

The efficacy variables include measurements or test results for individual subjects of the following:

- SARS-CoV-2 infection determined by RT-qPCR test of nasal swab and saliva samples: positive for infection defined as positive RT-qPCR result of either nasal swab or saliva; negative for infection defined as negative RT-qPCR of both nasal swab and saliva
- Viral shedding ($\log_{10}$ copies/mL) from RT-qPCR test
- Asymptomatic SARS-CoV-2 infection based on strict term: positive RT-qPCR result of either nasal swab or saliva without any of the strict-term SARS-CoV-2 infection signs and symptoms (specified in Section 9.2.2.2) within the EAP
- Asymptomatic SARS-CoV-2 infection based on broad term: positive RT-qPCR result of either nasal swab or saliva samples without any of the broad-term SARS-CoV-2 infection signs and symptoms (specified in Section 9.2.2.2) within the EAP
- Symptomatic infection based on strict-term SARS-CoV-2 infection signs and symptoms (for primary endpoint): Positive strict-term symptomatic infection defined as when SARS-CoV-2 infection signs and symptoms (specified in Section 9.2.2.2) and a positive RT-qPCR occur within the EAP
- Symptomatic infection based on broad-term SARS-CoV-2 infection signs and symptoms (for secondary endpoints): Positive broad-term symptomatic infection defined as when SARS-CoV-2 infection signs and symptoms (specified in Section 9.2.2.2) and a positive RT-qPCR occur within the EAP
- Medically attended visits to ED or UCC due to SARS-CoV-2 infection.
- Hospitalization due to SARS-CoV-2 infection (hospitalization status and days in hospital)
- Days absent from daily responsibilities (eg, days missed from work, school, childcare, or eldercare) due to SARS-CoV-2 infection
- Occurrence of laboratory-confirmed COVID-19 infection during follow-up period collected from spontaneously reported AEs

Detailed descriptions for assessing COVID-19 signs and symptoms and their temporal relationship with lab confirmed SARS-CoV-2 infection is provided in Section 9.2.2.2.

5.3. Safety Variables

Safety variables include recording, measurements, or laboratory test results for individual subjects of the following: TEAEs; vital signs including heart rate, blood pressure, respiration rate, and body temperature, physical examination findings; results of laboratory tests including hematology, blood chemistry, and urinalysis.

5.4. Pharmacokinetic Variables

The pharmacokinetic variables are the concentrations of REGN10933 and REGN10987 and time. The sampling timepoints for dense and sparse collection schedules are specified in Table 2.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples in this study will be collected at the clinic visits specified in Table 2.

6. STUDY DESIGN

6.1. Study Description and Duration

This is a phase 3 randomized, double-blind, placebo-controlled study in adults with household contact exposure to individuals with SARS-CoV-2 infection. This study is designed to assess the efficacy of the administration of REGN10933+REGN10987 to reduce the incidence of SARS-CoV-2 infection and prevent the development of disease (symptomatic SARS-CoV-2 infection) after household exposure to individuals with SARS-CoV-2 infection. Safety, tolerability, PK, and immunogenicity of REGN10933+REGN10987 will also be evaluated.

Eligible subjects are those who are asymptomatic and household contacts with sustained close exposure (at least 48 hours) with an individual with SARS-CoV-2 infection (index case). Randomization will be performed by individual study subjects, not by households.

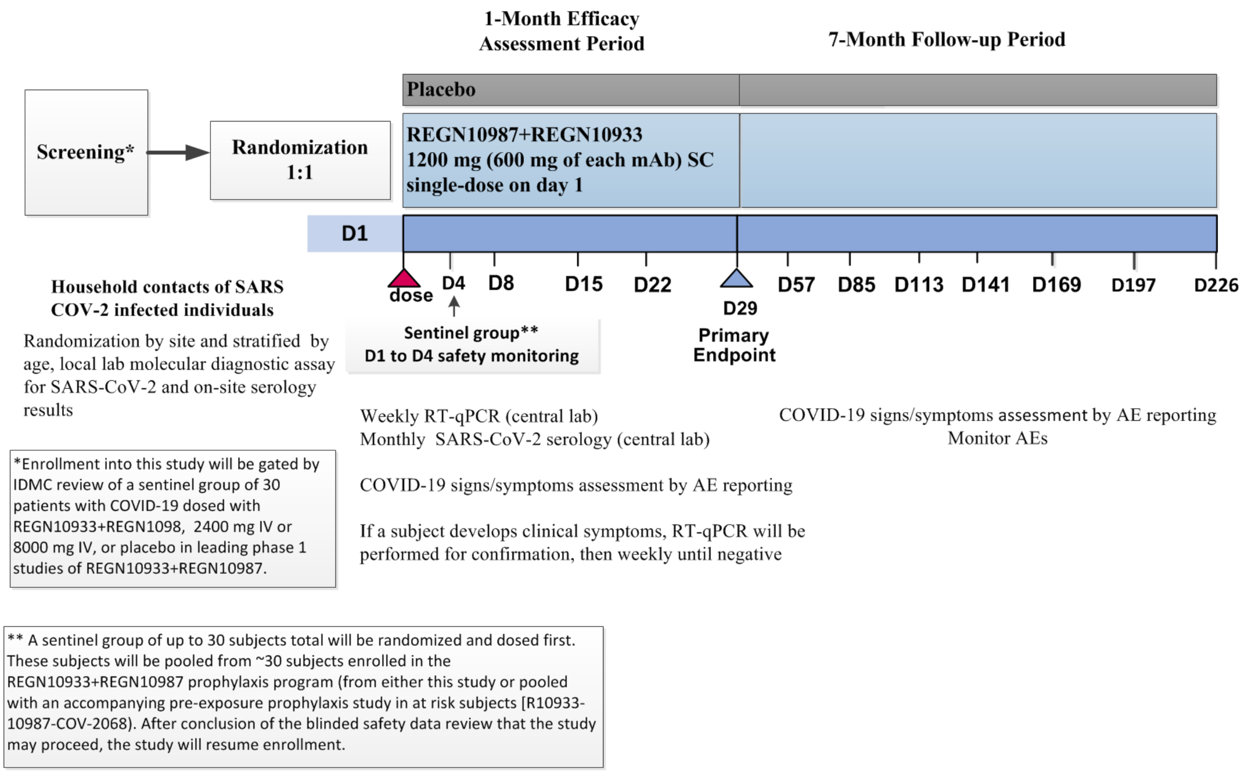
Approximately 2000 subjects will be enrolled. Randomization will be performed by site and stratified for assignment of treatment group by test results of local molecular diagnostic assay for SARS-CoV-2 from respiratory samples and on-site LFIA serology assay, and age group (≥50 or <50) (Section 8.4). Cohort allocation will be based on central lab baseline SARS-CoV-2 RT-qPCR for data analysis: cohort A (negative) and cohort B (positive) (defined in Section 6.1.5). Approximately 1700 subjects are planned to be enrolled in cohort A and 300 subjects in cohort B. Statistical analyses will be conducted separately in each cohort. For the purpose of the study analysis, cohort A and cohort B are independent.

Subjects will be randomized in a 1:1 allocation ratio to 1 of 2 treatment groups (placebo or REGN10933+REGN10987) (Section 8.1).

For each subject, the study comprises 3 periods: a 1-day screening/baseline period, a 1-month EAP, and a 7-month follow-up period.

The study flow diagram is provided in Figure 1.

Figure 1: Study Flow Diagram



6.1.1. Sentinel Subjects and Staggered Enrollment/Dosing:

Enrollment into this study will be gated by IDMC review of a sentinel group of 30 patients with COVID-19 dosed with REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 8000 mg IV or placebo in leading phase 1 studies of REGN10933+REGN10987 (Section 3.2.4).

Enrollment in this study will be carried out in 2 phases:

1. Sentinel group will comprise ~30 subjects (by subject number assigned by IWRS; irrespective of allocation to cohort A or cohort B): These subjects will be pooled from ~30 subjects enrolled in the SC administered REGN10933+REGN10987 prophylaxis program (from either this study or pooled with an accompanying pre-exposure prophylaxis study in at risk subjects [R10933-10987-COV-2068]. Subjects will be monitored for safety on-site for a minimum of 4 hours after administration of the first dose of study drug and then daily via visits to the study site or phone calls for the first 4 days (96 hours). Because REGN10933+REGN10987 will already have cleared a sentinel safety group at higher doses administered IV in previous studies, the sentinel group in this study will a focus on safety evaluation for injection site reactions and hypersensitivity reactions and data will be reviewed before progressing with enrollment of additional study subjects. The blinded safety data review will be led by a designated member of the Regeneron clinical team (generally either the medical monitor or the clinical trial manager) and at a minimum the data review team will include the Regeneron Medical Monitor, Study Biostatistician, Global Patient Safety Lead or designee, and the Senior Vice President of Early Clinical Development & Experimental Sciences.

2. Following a conclusion of the blinded safety data review that the study may proceed, the study will resume enrollment.

In case of any safety concerns, the IDMC may be consulted and requested to provide recommendations.

6.1.2. Screening/Baseline

After subjects provide informed consent, they will be assessed for study eligibility. The screening visit and randomization visits occur on the same day. Subjects will be provided with contact information for the clinical study site and will be given written and verbal instructions to call site personnel with any changes in their health status.

On day 1, prior to randomization, a local molecular diagnostic assay for SARS-CoV-2 RT-PCR from respiratory samples and local serology assay for anti-SARS-CoV-2 will be performed. The results of these assays will be used as stratification factors for randomization to treatment groups (placebo or REGN10933+REGN10987). Nasal swab and saliva samples for central lab testing of SARS-CoV-2 RT-qPCR and blood sample for central lab serology will be collected and sent to central lab. After completing baseline assessments and sample collection, all subjects will receive a single-dose of study drug (see details of study drug administration in Section 8.1). The central lab results of baseline SARS-CoV-2 RT-qPCR will be used to allocate subjects into cohort A (negative result) or cohort B (positive result).

Subjects in the sentinel group will be monitored for vital signs and TEAEs in the clinic for at least 4 hours after dosing on day 1 and then daily by phone call or site visit until day 4 (96 hours).

During post-dose monitoring, Grade 3 or greater injection site reactions and hypersensitivity reactions that occur after study drug administration will be captured as an AESI to allow for expedited reporting to the sponsor (see AE grading system in Section 10.2.4 and list of AESIs in Section 10.1.3).

6.1.3. Efficacy Assessment Period (EAP)

Efficacy, safety, sample collections, and other study assessments will be performed at specified time points throughout the EAP according to the Schedule of Events specified in Section 9.1. On day 1/baseline with study drug administration, sample collection must occur prior to study drug administration.

If subjects are able to travel and can do so while maintaining social distancing guidelines, subsequent site visits will be conducted; alternatively, telemedicine visits, phone calls, mobile units or home health nurses may be utilized. Throughout the study, biological samples will be obtained by adequately trained and delegated study personnel at study locations where appropriate personal protective equipment (PPE) are available to be used.

At each weekly visit, assessments and procedures will be performed (Table 1 and Table 2). The nasal swab and saliva samples will be collected for SARS-CoV-2 RT-qPCR to be tested at the central lab. The investigator or designee will contact each subject weekly (site visit or telemedicine) to assess the subjects general health, and to document AEs in general and any signs and symptoms associated with SARS-CoV-2 infection since the last contact (see details of the procedure in Section 9.2.2.2).

Any subject who develops fever, an acute respiratory illness or other symptoms that they may feel could be related to COVID-19 should alert the study staff immediately. Subjects' symptoms must be evaluated by the investigator or designee, which can occur through site visit, mobile unit, home visit, telemedicine, etc. If investigator or designee suspects SARS-CoV-2 infection, both nasal swab and saliva samples should be collected and sent for central lab testing. The subject may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1).

Subjects with laboratory confirmed SARS-CoV-2 infection should be informed as soon as possible and should undergo medical isolation to prevent contact with others to reduce the risk of further transmission. Since these subjects will likely be isolated, the study visits, assessments and sample collections may occur through a variety of methods.

For subjects who are positive for SARS-CoV-2 at any time during the EAP, including those positive at baseline, subsequent assessments/sample collections in the EAP should follow that specified in Table 1 until 2 consecutive confirmed negative SARS-CoV-2 RT-qPCR test results ≥24 hours apart. A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

Subjects presenting with acute illness should be medically managed according to local standard of care as per the discretion of the treating physician.

If a subject is hospitalized for suspected COVID-19, every effort should be made by the site personnel to collect, as soon as possible, nasal swab and/or saliva samples for central lab SARS-CoV-2 RT-qPCR testing. In subjects where it is not possible to have samples collected for assessment in the central laboratory, study site personnel will obtain and record information about all SARS-CoV-2 assays conducted in other medical facilities, including result(s), name of the assay(s) and whether the laboratory(ies) conducting the assays is a CLIA (Clinical Laboratory Improvement Amendments) certified (or equivalent) laboratory. After discharge, as described above, all subjects with a positive SARS-CoV-2 RT-PCR will continue to follow the weekly planned study visits until 2 confirmed negative SARS-CoV-2 RT-qPCR test results are achieved at least 24 hours apart.

6.1.4. Follow-up Period

Subjects who remain SARS-CoV-2 RT-qPCR negative throughout the EAP will complete the end of the EAP and enter the Follow-up Period to be followed for 7 months (Table 1, Table 2).

Subjects who become SARS-CoV-2 RT-qPCR positive during the EAP will continue to have weekly nasal swab and saliva samples for SARS-CoV-2 RT-qPCR test until 2 confirmed negative SARS-CoV-2 RT-qPCR test results are achieved at least 24 hours apart, even after they complete the EAP and enter the study Follow-up Period to be followed for 7 months. In such situations, these visits for sample collection in the Follow-up Period should be characterized as unscheduled visits. A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

At each scheduled visit, the investigator or designee will contact each subject (site visit or telemedicine) to assess and document the subject's general health, AEs in general and signs and symptoms associated with SARS-CoV-2 infection since the last contact as described for the EAP (Section 6.1.3).

Any subject who, between the study visits, develops fever, an acute respiratory illness or other symptoms that they may feel could be related to COVID-19 should alert the study staff immediately. The subjects' symptoms must be evaluated by the investigator or designee, which can occur through site visit, mobile unit, home visit, telemedicine, etc. If the investigator or designee deems the subject's signs/symptoms require the collection of biological samples for central lab testing to assess or confirm SARS-CoV-2 infection, the subject will be advised to provide nasal and saliva samples. The subject may also be asked to provide a blood sample if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1).

6.1.5. Description of Study Cohorts

The study has 2 independent cohorts, cohort A and cohort B.

All subjects enrolled in the study will be household contacts of a SARS-CoV-2 infected individual and asymptomatic at the time of screening. The subjects' SARS-CoV-2 infection status, positive or negative by SARS-CoV-2 RT-qPCR (central lab) at baseline, determines the study procedures they follow (SOE) and the analysis of endpoints.

- **Cohort A SARS-CoV-2 RT-qPCR Negative at Baseline:** Approximately 1700 adult subjects with a negative SARS-CoV-2 RT-qPCR result includes subjects who are asymptomatic at baseline. Cohort A will evaluate the efficacy of a single-dose of REGN10933+REGN10987 as prophylaxis to prevent SARS-CoV-2 infection. The primary efficacy analyses will be conducted with cohort A.
- **Cohort B SARS-CoV-2 RT-qPCR Positive at Baseline:** Approximately 300 adult subjects with a positive SARS-CoV-2 RT-qPCR result includes subjects who are asymptomatic with a positive SARS-CoV-2 infection status by RT-qPCR (central lab) at baseline. Cohort B will evaluate the effect of a single-dose of REGN10933+REGN10987 as preemptive therapy to prevent or modify symptomatic disease. Cohort B is intended for secondary and exploratory analyses.

Study objectives and endpoints are specified for each cohort (Section 2 and Section 4).

The statistical analysis sets for the cohorts are defined in Section 11.3.1.

6.1.6. Study Stopping Rules

6.1.6.1. Study Stopping Criteria

The IDMC, which may also be referred to Data and Safety Monitoring Board (DSMB), will monitor unblinded data on a regular basis to assess the risk/benefit profile of REGN10987+REGN10933. If at any time the IDMC has significant concerns regarding a meaningful imbalance in TEAEs or treatment-emergent SAEs, the IDMC may make a recommendation to the Sponsor to halt the study or make recommendations for other changes in the study conduct. This will prompt a review by the Sponsor who will decide to implement, modify, or reject the recommendation. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

Pre-specified stopping rules for early termination of the study for efficacy will be documented in the Statistical Analysis Plan and IDMC Charter.

6.1.7. End of Study Definition

The end of study is defined as the date the last subject completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study subject can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

Due to the novel nature of the COVID-19 pandemic, efficacy endpoints and associated assumptions are not well established, especially the anticipated attack rate resulting in SARS-CoV-2 RT-PCR positivity within a household and the proportion of cases that will progress to symptomatic disease, interim analyses will be conducted by the IDMC

Decision rules will be specified in the Statistical Analysis Plan and in the IDMC Charter.

A formal interim efficacy analyses may be conducted when 50% of subjects complete the EAP visit for the primary endpoints. A sample size re-estimation may be carried out when 25% of originally planned number of subjects complete EAP visit for the primary endpoints.

A description of the statistical methods to be employed is in Section 11.5, and blinding implications are discussed in Section 8.5.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

The terms IDMC and DSMB employed during the conduct of this study refers to the safety committee that will perform safety monitoring for this study and the terms are interchangeable in this protocol.

The IDMC, which may also be referred to Data and Safety Monitoring Board (DSMB), will be utilized to evaluate the safety of REGN10933+REGN10987 on a regular basis. The IDMC is important for this prophylaxis study, given the limited amount of safety data currently available, and because the study will enroll a large number of adults. The IDMC may also be asked to perform a formal interim evaluation of efficacy (Section 11.5) and/or sample size re-estimation to be conducted when 25% of the originally planned number of subject complete the EAP (Section 11.2.1). The details of such evaluation will be described in the IDMC Charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

7.1. Number of Subjects Planned

Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline- Approximately 1700 adult subjects will be enrolled. Cohort A is expected to include the majority of study subjects.

Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline- Approximately 300 adult subjects will be enrolled.

7.2. Study Population

Eligible subjects for this study consist of asymptomatic, healthy adults who are household contacts to an individual with a positive SARS-CoV-2 RT-PCR assay (index case).

7.2.1. Inclusion Criteria

A subject must meet the following criteria to be eligible for inclusion in the study:

1. 18 years of age and above at the signing of informed consent
2. Asymptomatic household contact with sustained exposure (at least 48 hours) to an individual with a positive SARS-CoV-2 RT-PCR assay (index case). To be included in the study, subjects must be randomized within 96 hours of collection of the index cases' positive SARS-COV-2 RT-PCR sample
3. Subject anticipates living in the same household with the index case until study day 29
4. Is judged by the investigator to be in good health based on medical history and physical examination at screening/baseline
5. Willing and able to comply with study visits and study-related procedures/assessments.
6. Provide informed consent signed by study subject or legally acceptable representative.

7.2.2. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Subject-reported history of prior positive SARS-CoV-2 RT-PCR test or positive SARS-CoV-2 serology test at any time before the screening
2. Subject has lived with individuals who have had previous SARS-CoV-2 infection
3. Active respiratory or non-respiratory symptoms consistent with COVID-19
4. History of respiratory illness with sign/symptoms of SARS-CoV-2 infection, in the opinion of the investigator within the prior month to screening
5. Nursing home resident
6. Any physical examination findings, and/or history of any illness, concomitant medications or recent live vaccines that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by their participation in the study

7. Current hospitalization or was hospitalized (ie, >24 hours) for any reason within 30 days of the screening visit
8. Has a history of significant multiple and/or severe allergies (eg, latex gloves), or has had an anaphylactic reaction to prescription or non-prescription drugs or food. This is to avoid possible confounding of the safety analysis and not due to any presumed increased risk of these individuals to a reaction to the investigational product
9. Treatment with another investigational agent in the last 30 days or within 5 half-lives of the investigational drug, whichever is longer, prior to the screening visit
10. Received an investigational or approved SARS-CoV-2 vaccine
11. Received investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (eg, convalescent plasma or sera, monoclonal antibodies, hyperimmune globulin)
12. Use of hydroxychloroquine/chloroquine, remdesivir, or other anti-SARS-CoV-2 viral agents within 60 days of screening
13. Member of the clinical site study team and/or immediate family
14. Sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study drug follow-up period and for 6 months after single dose of study drug: vasectomy with medical assessment of surgical success OR consistent use of a condom. Sperm donation is prohibited during the study and for up to 6 months after the last dose of study drug.
15. Pregnant or breastfeeding women.
16. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
    c. bilateral tubal ligation

    *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial

Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

7.3. Premature Withdrawal from the Study

A subject has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or Sponsor have the right to withdraw a subject from the study if it is no longer in the interest of the subject to continue in the study, or if the subject's continuation in the study places the scientific outcome of the study at risk (eg, if a subject does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Subjects who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.3.

7.4. Replacement of Subjects

Subjects prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The following drug product will be provided. Instructions on dose preparation are provided in the pharmacy manual.

REGN10933 and REGN10987, to be co-administered:

- REGN10933: Supplied as a 120 mg/mL solution for SC injection
- REGN10987: Supplied as a 120 mg/mL solution for SC injection

Matching placebo:

- Supplied as matching solution for SC injection.

All subjects will receive 4 SC injections of study drug on day 1, each containing 2.5 mL of active study drug or placebo.

It's recommended that SC injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs. During the dose administration, each injection must be given in a different anatomical location (eg, 1 injection administered in the right lower quadrant of the abdomen, another in the left lower quadrant of the abdomen, etc).

A pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will prepare the drug for SC administration. The prepared syringe must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and subject.

8.2. Dose Modification and Study Treatment Discontinuation Rules

8.2.1. Dose Modification

This is a single dose study; dose modification is not allowed.

8.2.2. Study Drug Discontinuation

This is a single dose study; study drug discontinuation is not applicable.

8.3. Management of Acute Reactions

8.3.1. Acute Injection Reactions

8.3.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4.

Acute systemic reactions following injection of study drug (subcutaneous [SC]) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.3.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4.

8.4. Method of Treatment Assignment

Subjects will be randomized in a 1:1 ratio to receive REGN10987+REGN10933 or placebo according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be performed by individual study subjects, not by households. All subjects randomized will be given a household identification number in the case that multiple members of the same household are enrolled and receive study drug. This ensures that any correlation among subjects within the same household may be considered in the statistical analysis.

- **REGN10987 and REGN10933**: 1200 mg (600 mg of each mAb) SC single dose on day 1
- **Matching placebo**: SC single dose on day 1

Randomization will be performed by site and stratified as follows:

- Local molecular diagnostic assay for SARS-CoV-2 from respiratory samples (positive, negative, or unavailable)
- Baseline serological status for SARS-CoV-2 based on on-site serology test (seropositive, seronegative, unavailable)
- Age ≥50 year (yes vs no)

Note that the cohorts used in the analysis are defined by the baseline central lab SARS-CoV-2 RT-qPCR results, not by the local molecular diagnostic assay.

8.5. Blinding

Study subjects, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Medical/Study Director, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all subject randomization assignments.

One or more interim analyses may be conducted (Section 11.5). No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the final database is locked for this study.

The study site staff who performs the on-site serology tests required for subject stratification will be unblinded to the serologic status of the subjects and therefore will be restricted to perform unblinded tasks only.

Anti-drug antibody, drug concentration results, and central lab serology results will not be communicated to the sites, and the Sponsor's blinded study team will not have access to results associated with subject identification until after the database is locked for the respective study part.

8.6. Emergency Unblinding

Unblinding of treatment assignment for a subject may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the subject's treatment assignment.

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected subjects will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the subject. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the subject

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the subject's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed at the site with approval by the Sponsor or returned to the Sponsor or designee.

8.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each subject
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.7.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the Sponsor and regulatory agency inspectors.

8.8. Concomitant Medications

Any treatment administered from the single dose of study drug to final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

8.9. Prohibited Medications

Treatment with the following concomitant medications as prophylaxis is prohibited in uninfected subjects or for treatment of asymptomatic infection during the EAP and Follow-Up Period and may result in permanent discontinuation from the study.

1. Other investigational drugs
2. Investigational or approved SARS-CoV-2 vaccine

3. Investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (eg, convalescent plasma or sera, monoclonal antibodies, hyperimmune globulin)
4. Hydroxychloroquine/chloroquine, remdesivir, or other anti-SARS-viral agents

8.10. Permitted Medications

Other than the prohibited medications listed in Section 8.9, treatment with concomitant medications is permitted during the study. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

Subjects with symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the study will be treated according to local standard of care as per the discretion of the investigator or treating physician. Any medication used by the study subject should be captured in the concomitant medication eCRF.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1 for the period from screening/baseline to end of the EAP and the Follow-up Period, and in Table 2 for sample collection for assay of drug concentration and ADA, as well as for safety clinical lab during the entire study.

Refer to Section 6.1.3 for conducting study assessments and sample collection when a subject is positive for SARS-CoV-2 infection based on rapid RT-PCR or RT-qPCR and when a subject is hospitalized.

Table 1: Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive)

Visit	Screening / Baseline[1]	Additional Safety (Sentinel Only)[2]				Efficacy Assessment Period (EAP)[3]				Follow-up Period							ET	Unscheduled Visit[4]
Visit Location Site (S), Phone (P)[5]	**S**	**S**	**S**	**P[14]**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**		
Visit Number	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS**		
Day	1	1	2	3	4	8	15	22	29	57	85	113	141	169	197	226		
Week	0	0	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)						±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Screening/Baseline:																		
Inclusion/exclusion	X																	
Informed consent	X																	
Informed consent for PGx sub-study(optional)[6]	X																	
Medical history	X																	
Demographics and risk factors for SARS-CoV-2 infection	X																	
Respiratory sample, molecular diagnostic assay for SARS-CoV-2 (local lab)	X[7]																	
Randomization	X																	
Serum, On-site serology LFIA (anti-SARS-CoV-2 antibodies)[8]	X																	
Treatment:																		
Study drug administration	X[9]																	
Efficacy (Virology):																		
Nasal swab, SARS-CoV-2 RT-qPCR (central lab)[9]	X[6]					X	X	X	X	Collect only when symptomatic[4]							X	X
		RT-qPCR positive subjects only: weekly until end of EAP, then weekly until 2 consecutive negative (≥24 hr) RT-qPCR[3,10]																
Saliva sample, SARS-CoV-2 RT-qPCR (central lab)[9]	X[6]					X	X	X	X	Collect only when symptomatic[4]							X	X
		RT-qPCR positive subjects only: weekly until end of EAP, then weekly until 2 consecutive negative (≥24 hr) RT-qPCR[3,10]																
Efficacy (Subject-Reported):																		
Assessment of ED, UCC, hospital visits						X	X	X	X	X	X	X	X	X	X	X		
						RT-qPCR positive subjects only: Complete weekly until COVID-19 related symptoms resolve												
Absenteeism assessment	X					X	X	X	X							X		
Safety:																		
Vital signs	X[2,11]	X[2]							X							X		X
Targeted PE[12]	X		X		X				X							X		X
Adverse events[16]	X	X[2]	X[2]	X[2]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
		For subjects with symptomatic SARS-CoV-2 infection, weekly until COVID-19 related symptoms resolve, otherwise per schedule																
Con Meds, Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Urine pregnancy test for WOCBP (dipstick, local lab)[13]	X								X							X		X
Laboratory Testing[14]:																		
Clinical Laboratory, Hematology, Blood Chemistry, Urinalysis	Refer to Table 2																	
Pharmacokinetics and Immunogencity[14]:																		
Drug concentration	Refer to Table 2																	
Anti-drug antibodies (ADA)																		
Biomarkers:																		
Serum for serology (central lab)[15]	X								X	X						X		
Research plasma	X								X	X						X		
						RT-qPCR positive subjects only												
Research serum	X								X	X						X		
Pharmacogenomics Sub-Study:																		
Whole Blood for RNA (Optional)[6]	X								X	X						X		
						RT-qPCR positive subjects only												
Whole Blood for DNA (Optional)[6]	X																	

EAP, Efficacy assessment period; EOS, end of study; ED, emergency departments; ET, Early termination; UCC, urgent care centers; LFIA, Lateral flow immunoassay; PE, physical exam; PGx, pharmacogenomics; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

9.1.1. Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes

1. The screening visit and baseline visit both occur on the same day.
2. The sentinel group will have additional safety monitoring on day 1 and through day 4.

   Vital signs: On day 1, vital signs (blood pressure, pulse rate and respiratory rate) will be measured at predose, approximately every 30 minutes during the first 2 hours after dose, at hour 3, and at hour 4 before dismissal.

   Adverse Events (injection site reactions and hypersensitivity): after the administration of the first dose of study drug, subjects will be monitored on site for a minimum of 4 hours and then by daily visits to the study site or phone calls for the first 4 days (96 hours), particularly focusing on the assessment of injection site reactions and hypersensitivity after study drug administration.
3. Subjects who have a positive RT-PCR result during screening, or who have a positive RT-qPCR result any time after screening, will have the additional assessments done as indicated (**RT-qPCR positive subjects only**). A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

   For subjects who become RT-qPCR positive after screening, the visit schedule will proceed as follows: (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.
4. Unscheduled visits: If, at any time after randomization until end of study, a subject develops fever, an acute respiratory illness or other symptoms they may feel could be related to COVID-19 or is hospitalized for suspected COVID-19, the subject should alert the investigator or designee immediately who will assess the subject's symptoms and condition (can be performed by phone contact, telemedicine, online meeting, home health care, etc) to decide if the subject should have an unscheduled visit for collection of nasal swab and saliva samples for RT-qPCR testing. The subject may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1). The investigator or designee should query the subject about AEs in general and AEs consistent of COVID-19 and record the information on CRF (see detailed description of the procedure in Section 9.2.2.2).

   (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window

(±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

5. Visit may occur by phone or electronic means
6. Separate consent is required for participation in the optional genomic sub-study and collection of blood samples for DNA and RNA. The sample for RNA, should be collected on day 1/baseline (pre-dose). Genomic DNA should be collected on day 1/baseline. If not collected at baseline, the sample for genomic DNA may be collected at any visit.
7. Sample for molecular diagnostic assay for SARS-CoV-2 (local lab) and RT-qPCR (saliva and nasal swab; central lab) should be collected before administration of study drug. The remnant samples may additionally be used for exploratory viral RNA sequencing and viral infectivity analyses.
8. Test kit will be provided to sites for this on-site serology test for anti-SARS-CoV-2 IgG/IgM (LFIA test). The test result will be provided only to the unblinded staff who will perform randomization and no other study activities; the test result will remain blinded to all other blinded study staff.
9. Study drug should be administered after all biological samples at screening/baseline have been collected.
10. Subjects who are RT-qPCR positive at the end of the EAP will continue to have samples collected weekly (nasal swab, saliva; central lab) for RT-qPCR. Subjects will continue assessments/sample collections until 2 negative RT-qPCR test results have been obtained ≥24 hours apart (all samples must be negative).
11. For subjects who are not in the sentinel group, vital signs will be monitored on site for 30 minutes after study drug administration.
12. The investigator may perform a targeted physical exam, request an exam and/or vital signs at any time. These assessments can be performed using a clinic visit or a remote delegate such as a home health aide.
13. For <u>all</u> women of childbearing potential (WOCBP). If the **local** urine pregnancy test is positive, the site must perform a serum pregnancy test at **central lab** for confirmation prior to randomization at baseline and prior to study drug administration. Subjects with confirmed pregnancy by central lab serum test should not be randomized or should be permanently discontinued from study drug for already randomized subjects.
14. Samples for drug concentration and, immunogenicity, and laboratory testing will be collected based on subset designation as indicated in Table 2
15. The serology test results will not be communicated to the sites, and the sponsor's blinded study team will not have access to results associated with subject identification until after the database is locked.
16. During each scheduled or unscheduled visit/contact, the investigator or designee will query subject about AEs in general (see Section 10) and evaluate if the AEs are associated with

SARS-CoV-2 infection (see Section 9.2.2.2). Subjects with symptomatic SARS-CoV-2 infection should be queried on their symptoms weekly until symptoms resolve, even during follow-up period, then follow the regular schedule.

Table 2: Schedule of Events for Drug Concentration, Immunogenicity, and Laboratory Testing

Samples for drug concentration (dense PK, sparse PK), immunogenicity assessment (ADA), and clinical laboratory testing (hematology, blood chemistry, and urinalysis) will be collected based on subset designation using subject number (assigned by IWRS):

- **Sentinel Group (Subset 1)**: First 30 subjects
- **Subset 2:** 31st to 400th subject
- **Subset 3:** 401st to 2000th subject

Visit	Screening / Baseline[1]	Sentinel Group Only		Efficacy Assessment Period (EAP)				Follow-up Period							ET Visit[5]	Unscheduled Visit
Site (S)	S	S	S	S	S	S	S	S	S	S	S	S	S			
Visit Number	1	2	4	5	6	7	8	9	10	11	12	13	14	EOS 15		
Day	1	2	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)				±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Sentinel Group (Subgroup 1)																
Dense PK[2]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X6
ADA[2,3]	X[1]						X			X		X		X	X	X[6]
Hematology[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Blood chemistry[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Urinalysis[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Subgroup 2																
Sparse PK[2]	X[1]						X	X		X		X		X	X	X[6]
ADA[2,3]	X[1]						X			X		X		X	X	X[6]
Hematology[4]	X[1]						X	X	X	X	X	X	X	X	X	
Blood chemistry[4]	X[1]						X	X	X	X	X	X	X	X	X	
Urinalysis[4]	X[1]						X	X	X	X	X	X	X	X	X	
Subgroup 3																
PK																X[6]
ADA[2,3]	X[1]						X			X		X		X	X	X[6]
Hematology[4]	X[1]						X									
Blood chemistry[4]	X[1]						X									
Urinalysis[4]	X[1]						X									

ADA, anti-drug antibodies; EAP, Efficacy assessment period; EOS, end of study; ET, Early termination; PK, Pharmacokinetics

9.1.2. Schedule of Events Table 2: Drug Concentrations, Immunogenicity, and Laboratory Testing

1. Samples should be collected before the administration of study drug. Administration of study drug must be performed on the on same day as sample collection.
2. Actual dosing time and dense PK, sparse PK, and ADA sample collection times will be recorded.
3. At the screening/baseline visit, the window for baseline pre-dose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
4. Samples will be analyzed at central lab.
5. Subjects who prematurely discontinue the study should have sample collection listed in the early termination (ET) visit before exiting the study.
6. A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

9.1.3. Early Termination Visit

Subjects who are withdrawn from the study will be asked to provide final blood samples for drug concentration and immunogenicity analysis.

9.1.4. Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, for SARS-CoV-2 RT-qPCR and serology testing when subjects experience symptoms consistent with SARS-CoV-2 infection (per the broad-term list specified in Section 9.2.2.2), or for any other reason, as warranted.

9.2. Study Procedures

This section describes the procedures and collections that will be performed in this study. Procedures and collections will occur according to the schedule of events (Table 1 and Table 2).

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: demographics (eg, age, sex, race, weight, height, etc), medical history, local molecular diagnostic assay for SARS-CoV-2 from respiratory samples, and onsite serum serology for anti-SARS-CoV-2 (IgG/IgM by LFIA test), query for risk factors for SARS-CoV-2 infection (eg, first responder or healthcare worker; presence in outdoor or indoor crowed or public places [without keeping distance >6 feet] in the last 14 days, with or without a mask and/or eye protection; attendance to any social events with more than 10 people in the last 14 days, with or without a mask and/or eye protection; exposure to someone believed to have

COVID-19; exposure to someone diagnosed with COVID-19; receipt of influenza vaccine as of July 2020).

9.2.1.1. Informed Consent

Informed consent must be obtained according to the requirements described in Section 13.2. Optional informed consent may be obtained for participation in the pharmacogenomics sub-study (refer to Section 9.2.8 for more information on this sub-study).

9.2.1.2. Local Molecular Diagnostic Assay for SARS-CoV-2 from Respiratory Samples

The investigator or sub-investigator will verify that the subjects tests negative or positive for local molecular diagnostic assay for SARS-CoV-2 RT-PCR from respiratory samples and record the test result in the eCRF, specimen type (eg, nasal swab), assay type, and date of test.

9.2.2. Efficacy Procedures

9.2.2.1. Nasal Swab and Saliva SARS-CoV-2 RT-qPCR Test (Central Lab)

Nasal swab and saliva samples will be collected from subjects to determine presence or absence of SARS-CoV-2 virus and to determine the relative quantitation of viral RNA shedding. Detailed instructions for sample collections are in the laboratory manual provided to study sites. For each study subject, an attempt should be made to consistently collect nasal swab samples for SARS-CoV-2 RT-qPCR test from the same nostril during all sampling visits.

9.2.2.2. COVID-19 Symptomology (Strict Terms and Broad Terms)

During each scheduled or unscheduled visit/contact, the investigator or sub-PI investigator, or designee (ie, nurse practitioner in countries where allowed by local law) will query the subject about adverse events the subject is experiencing or has experienced since the last visit/contact (eg, within the prior week if it's a weekly scheduled visit) and ask about all of the signs and symptoms associated with these adverse events including the start date, end date and severity of each. The investigator should avoid querying the subject by running a check-list of signs and symptoms, but rather allow the subject to spontaneously report everything that they presented.

All signs and symptoms related to the AEs, along with the corresponding start date, end date and severity should be documented in the subject's medical records (source document). As signs and symptoms may appear and resolve on different days and may precede or occur after the collection of nasal swab and saliva samples for the SARS-CoV-2 RT-qPCR test, it is important that this detailed information be captured in the source document.

Independent of the results (positive or negative) of the SARS-CoV-2 RT-qPCR tests performed on samples collected from study subjects during the weekly or unscheduled visits, all adverse events must be documented in the AE CRF. Signs and symptoms related to the adverse events reported in the AE CRF and confirmed to be temporally related to a positive SARS-CoV-2 RT-qPCR test collected from the subject's nasal swab and/or saliva sample will be reported on a separate CRF (individual sign or symptom with start date and end date, and associated severity).

For the purpose of the study's primary and secondary objectives, the assessment of association of symptomatic disease with SARS-CoV-2 infection (ie, diagnosis of strict term COVID-19 and broad term COVID-19) will be based on the strict term and broad term COVID-19 definitions described below (Table 3) and the temporal relationship of the signs and symptoms with lab confirmed SARS-CoV-2 infection (based on central lab RT-qPCR test result).

Temporal Relationship of Signs and Symptoms with Positive RT-qPCR for Diagnosis of COVID-19

The onset date of signs/symptoms will utilize a ±14 days window from the date of the positive SARS-CoV-2 RT qPCR, so long as the signs/symptom onset does not precede a negative SARS-CoV-2 RT-qPCR test. That is, the onset date of symptomatic SARS-CoV-2 infection is defined as the date of the first sign/symptom that is consistent with a diagnosis of COVID-19 as determined by the investigator. The onset date must be after the last negative SARS-CoV-2 RT-qPCR and no more than 14 days prior to the first positive SARS-CoV-2 RT-qPCR or must occur on or before 14 days after the last positive SARS-CoV-2 RT-qPCR.

Strict-Term Definition of COVID-19 Signs and Symptoms used for the Primary Efficacy Endpoints:

As described in Section 4.1.1, the primary endpoint will utilize a strict definition of signs and symptoms of COVID-19 (see Table 3).

Broad-Term Definition of COVID-19 Signs and Symptoms used for Secondary Efficacy Endpoints:

The broad term COVID-19 signs and symptoms are defined as any of the 23 symptoms listed in Table 3 or fever (≥38°C).

Table 3: Strict-Term and Broad-Term COVID-19 Signs and Symptoms

Strict term defined by:	Broad term defined as any of the following:
Fever (≥38°C) PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath) *OR* 2 respiratory symptoms (sore throat, cough, shortness of breath) *OR* 1 respiratory symptom (sore throat, cough, shortness of breath) PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise)	• Fever ≥38°C • The signs and symptoms below: 1. Feverish 2. Sore throat 3. Cough 4. Shortness of breath/difficulty breathing *(shortness of breath)* 5. Chills 6. Nausea 7. Vomiting 8. Diarrhea 9. Headache 10. Red or watery eyes *(conjunctivitis)* 11. Body aches such as muscle pain or joint pain *(myalgia, arthralgia)* 12. Loss of taste/smell 13. Fatigue *(fatigue or general malaise)* 14. Loss of appetite 15. Confusion 16. Dizziness 17. Pressure/tightness in chest 18. Chest pain 19. Stomach ache 20. Rash 21. Sneezing 22. Runny nose 23. Sputum/phlegm 24. Other___________________

9.2.2.3. Assessment of Medically Attended Visits

Subjects who become SARS-CoV-2 RT-qPCR positive will be queried on any SARS-CoV-2 infection-related medically attended visits to the ED, UCC, or hospitalization starting from the timepoint of SARS-CoV-2 RT-qPCR positive and through the end of the EAP. Details associated with any SARS-CoV-2 infection-related medically-attended visit will be recorded and will include at minimum:

- Nature of the visit (ED, UCC, hospital stay)
- Date and length of visit
- Primary reason for the visit should be recorded as an adverse event

9.2.2.4. Absenteeism Assessment

In subjects with a positive SARS-CoV-2 RT-PCR, weekly assessments of absenteeism will be performed to assess absenteeism, defined as number of days missed for daily responsibilities, including work (employed adults) or school (matriculating students), or family obligations/responsibilities (childcare or eldercare) due to SARS-CoV-2 infection starting from the timepoint of SARS-CoV-2 RT-qPCR positive and through the end of the EAP.

9.2.3. Safety Procedures

9.2.3.1. Targeted Physical Examination and Vital Signs

The targeted physical examination and vital signs include measurements of temperature, blood pressure (measured after the subject has been resting quietly for at least 5 minutes and may be obtained from a seated or supine position), pulse rate, and respiratory rate, and examination of the oropharynx, skin, heart, lungs and any other system(s) depending on any complaints or concerns expressed by the subjects.

Vital signs consisting of blood pressure, pulse rate, and respiratory rate will be collected on day 1 pre-dose, approximately every 30 minutes during the first 2 hours after dose, at hour 3, and at hour 4 before dismissal in the sentinel group. Vital signs will be collected from all study subjects prior to administration of study drug and approximately 30 minutes post dose administration, and as needed, according to local standard of care as per the discretion of the investigator.

9.2.3.2. Laboratory Testing

Samples for laboratory testing will be collected at visits according to the Schedule of Events Table 2. Samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Urine pregnancy test will be performed for WOCBP at baseline and prior to administration of study drug. If a subject has a positive urine pregnancy test, a serum pregnancy test at the **central lab** should be performed. Subjects with serum test confirmed pregnancy should not be randomized. If there is positive pregnancy test during the study after receiving study drug, subject should be followed up until pregnancy outcome.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment **may** be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Drug Concentration and Measurements

Serum samples for REGN10933 and REGN10987 drug concentration measurement will be collected per the schedule of events in Table 2. A subset of the first 30 subjects (by subject number by IVRS) will have frequent sample collection (dense PK). The second subset will include the next 370 subjects (the 31st to 400th subjects) who will have less frequent sample collection (sparse PK). Any unused samples may be kept for up 15 years after study completion for use in exploratory research.

9.2.5. Immunogenicity Measurements and Samples

Immunogenicity will be assessed by ADA. Samples for ADA assessment will be collected for all subjects at time points listed in Table 2. Any unused samples may be kept for up 15 years after study completion for use in exploratory research.

9.2.6. Exploratory Pharmacodynamic/Biomarker Procedures

A description of planned or potential exploratory analyses is provided below. Samples for assessment of pharmacodynamic and exploratory biomarkers will be collected at time points indicated in Table 2. Residual serum or plasma samples collected for other purposes may also be used to study how REGN10933+REGN10987 work and SARS-CoV-2 infection, including but not limited to, cytokines, complement pathways, and other factors emerging to be associated with disease or clinical prognosis. Any unused samples may be kept for up 15 years after study completion for use in exploratory research.

9.2.6.1. Virology

9.2.6.1.1. Viral Sequencing

In support of public health initiatives to track SARS-CoV-2 genetic variants, viral genome sequencing will be performed on all viral nucleic acid isolated from nasal swab and/or saliva samples at baseline. Sequencing analyses will be of the entire viral genome, including the full gene sequence that encodes the SARSCoV-2 S protein.

The results of the viral sequencing will not be included in the clinical study report.

9.2.6.1.2. Viral Resistance

Subjects will be assessed for virologic resistance, defined as (1) those subjects who are positive at baseline and remain positive without a consistent decrease in viral load by 4 weeks, (2) those subjects who were negative and become positive during the EAP, and/or (3) those subjects who have 2 consecutive negative RT‑qPCR tests with a subsequent positive RT−qPCR test result. For subjects who exhibit viral resistance, viral sequencing will be performed to understand the potential relationship between genetic mutations and mAb functional activity. Viral sequencing may also be done on a gender-matched placebo control group in order to determine whether any genetic mutations observed in the mAb treatment group are naturally emergent genetic variants.

The results of the viral resistance will not be included in the clinical study report.

9.2.6.1.3. Viral Infectivity

To explore the effects of REGN10933+REGN10987 on infectivity of SARS-CoV-2, we may use viral culture assays or subgenomic viral mRNA transcript analyses. Subgenomic viral RNA transcripts potentially indicate the presence of actively replicating virus in samples, as viral subgenomic mRNA is transcribed only in infected cells and is not packaged into virions. These data may be associated to RT-qPCR data from matched samples for each group and compare to placebo or other clinical or other measures in the study.

9.2.6.2. Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies

In order to assess the impact of baseline humoral immunity/antibody response to SARS-CoV-2 on REGN10933+REGN10987 efficacy to prevent SARS-CoV-2 infection, serum anti-SARS-CoV-2 will be measured at baseline, including but not limited to those which detect antibodies against the S protein and/or the N protein and/or neutralization assays. The impact of a positive serology result on drug efficacy will be assessed by associating seropositivity to positive SARS-CoV-2 RT-qPCR test from nasal swabs and/or saliva. Association of seropositivity with clinical endpoints and other measures may also be explored.

To explore whether REGN10933+REGN10987 affect the generation of a humoral immune response to SARS-CoV-2, serum anti-SARS-CoV-2 N protein antibodies will be measured using immunoassays in REGN10933+REGN10987 groups as compared to placebo control, as well as to baseline.

Any unused samples may be kept for up 15 years after study completion for use in exploratory research.

9.2.7. Serum and Plasma for Research

Research serum and plasma are being collected and banked for exploratory research related to COVID-19, SARS-CoV-2, REGN10933+REGN10987, host and viral biological pathways and mechanisms related disease activity and clinical outcomes. The data from these exploratory analyses may not be included in the CSR.

9.2.8. Pharmacogenomic Analysis (Optional)

Subjects who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Blood sample for RNA must be collected predose on day 1. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose) but can be collected at a later study visit. DNA and RNA samples will be collected for pharmacogenomics analyses to understand the genetic and/or transcriptional determinants of efficacy and safety associated with the treatments in this study and the molecular basis of SARS-CoV-2 infection. These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomic analyses which the Sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN10933+REGN10987, other SARS-CoV-2 infection clinical outcome measures, and possible treatment-emergent adverse events. In addition, associations between genomic variants and prognosis or progression of SARS-CoV-2 infection as well as related viral pneumonia and respiratory diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic and transcriptional markers related to the study drug, target pathway, or SARS-CoV-2 infection. These data may also be combined with viral sequence analyses to study host/virus genetic interactions.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

Results from the genomic and transcriptional analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of study (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the Investigator assesses as related to study drug should also be reported.

All AEs, serious adverse events (SAEs), AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following: (as defined in Section 10.2.3):
  - Grade 3 or greater injection site reactions or hypersensitivity reactions including but not limited to anaphylaxis, laryngeal/pharyngeal edema, severe bronchospasm, chest pain, seizure, or severe hypotension (AE grading system is provided in Section 10.2.4)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male, during the study and for 8 months following administration of the single dose of study drug. Any complication of pregnancy affecting a female study subject or female partner of a male study subject, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a subject administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a subject is a passenger).
- Is **life-threatening** – in the view of the investigator, the subject is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-subject **hospitalization** or **prolongation of existing hospitalization**. In-subject hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Severity

The severity of AEs (including test findings classified as AEs) and injection-site -related reactions will be graded using the current version of the NCI–CTCAE v5.0 0 (Division of Cancer Treatment and Diagnosis (DCTD), 2020). The NCI-CTCAE severity grading systems for anaphylaxis, allergic reaction, and injection site reaction are specifically provided Table 4.

Table 4: NCI-CTCAE Severity Grading System for Adverse Events for Anaphylaxis, Allergic Reaction, and Injection Site Reaction

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anaphylaxis			Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death					
Allergic reaction (hypersensitivity reaction)	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Injection site reaction	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					

Source: (Division of Cancer Treatment and Diagnosis [DCTD], 2020)

10.2.5. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Subject's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, subject's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, subject's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, subject's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, subject's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study subject at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (REGN10933+REGN10987), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB unless delegated to the sponsor.

Event expectedness for study drug (REGN10933+REGN10987) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IRBs as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

The following null and alternate hypotheses will be tested for the primary and secondary endpoints:

H0: No treatment difference between REGN10933+REGN10987 and placebo

H1: There is a treatment difference between REGN10933+REGN10987 and placebo

11.2. Justification of Sample Size

11.2.1. Cohort A- Justification of Sample Size

In cohort A, subjects are randomized in a 1:1 allocation ratio to REGN10933+REGN10987 or placebo. There are 2 primary hypotheses: (1) the reduction in the proportion of symptomatic SARS-CoV-2 infections; and (2) the reduction in the proportion of symptomatic or asymptomatic SARS-CoV-2 infections. For the planning of sample size required to achieve at least 90% power, it is assumed that they will be tested in parallel at the 0.025 level (see Section 11.4.4 for details of multiplicity control). Note that both of these primary hypotheses are tested among those subjects who are seronegative at baseline.

In this household design, both the number of subjects per household and the correlation between subjects in infection rates within household are both unknown. If there is only 1 subject per household, a sample size of 1368 seronegative subjects provide approximately 90% power to detect a relative risk of 0.5 (ie, 50% reduction of the assumed 10% placebo attack rate) considering an interim analysis when 50% of subjects complete EAP (Section 11.5). Table 5 provides power calculations if the same number of subjects derives from 640 households (yielding an average household size of 2.14 subjects) with varying degrees of correlation within household. In all cases, the power of the study is >90%.

Table 5: Simulated Power for Household Design (1368 Subjects over 640 Households)

Placebo Attack Rate	REGN10933+ REGN10987 Attack Rate	Correlation within Household	Average Odds Ratio REGN10933+REGN10987 versus Placebo	Power
10%	5%	0.1	0.489	0.950
10%	5%	0.2	0.473	0.965
10%	5%	0.3	0.485	0.960
10%	5%	0.4	0.459	0.980
10%	5%	0.5	0.486	0.990

In order to obtain 1368 subjects in cohort A, approximately 1700 subjects will need to be enrolled, assuming that 10% of subjects drop out and 10% of subjects are seropositive at baseline. These power calculations also assume that the attack rate is 10% and 5% in placebo and REGN10933+REGN10987 groups, respectively, for both primary efficacy endpoints.

Since the number of subjects per household and the correlation among subjects within each household are both unknown, a sample re-estimation will be conducted by the IDMC after approximately 10% to 25% of subjects have completed the EAP.

11.2.2. Cohort B - Justification of Sample Size

The key secondary endpoint in cohort B is the reduction in the proportion of subjects who develop signs and symptoms (strict-term) of symptomatic SARS-CoV-2.

The sample size of cohort B assumes that approximately 15% of subjects in a household are already positive for SARS-CoV-2 by RT-qPCR at baseline. Therefore, among 2000 subjects enrolled in this study in order to obtain 1700 subjects for cohort A, the number of subjects expected in cohort B is approximately 300. Assuming that there would only be 1 subject per household and that 50% will develop symptoms, cohort B will provide >95% power to detect a relative risk of 0.5 (ie, 50% risk reduction) using a 2-sided Fisher's exact test at alpha level of 0.05.

11.3. Analysis Sets

11.3.1. Full Analysis Set

Cohort A Full Analysis Set

The full analysis set for cohort A (FAS-A) includes all randomized subjects based on the treatment allocated (as randomized) who have laboratory confirmed negative tests for SARS-CoV-2 RT-qPCR and SARS-CoV-2 serology (both based on central lab testing). The primary efficacy endpoints and the secondary efficacy endpoints for cohort A will be analyzed using the FAS-A unless specified otherwise.

Cohort B Full Analysis Set

The full analysis set for cohort B (FAS-B) includes all randomized subjects based on the treatment allocated (as randomized) who are laboratory confirmed positive at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing). The efficacy endpoints for cohort B will be analyzed using the FAS-B unless otherwise specified.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized subjects who received at least 1 dose or part of a dose of study drug. Subjects in SAF will be analyzed based on the treatment received (as treated) by study cohort.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all subjects who received any study drug and who had at least 1 non-missing drug concentration measurement following the first dose of study drug. Subjects will be analyzed based on actual treatment received.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all subjects who received study drug and had at least 1 non-missing ADA result from the ADA assay after first dose of the study drug. Subjects will be analyzed according to the treatment actually received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of subjects reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Baseline is defined as the last assessment obtained before the first dose of study drug.

11.4.1. Subject Disposition

The following will be provided:

- The total number of screened subjects, defined as originally having met the inclusion criteria and signed the ICF
- The total number of randomized subjects: received a randomization number
- The total number of subjects randomized but not receiving study treatment
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- The total number of subjects who discontinued from study treatment, and the reasons for discontinuation
- A listing of subjects treated but not randomized, subjects randomized but not treated, and subjects randomized but not treated as randomized
- A listing of subjects prematurely discontinued from the study, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all subjects combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

11.4.3.1.1. Primary Efficacy Analysis (Cohort A)

The primary efficacy endpoints described in Section 4.1.1 will be analyzed in the FAS-A population. In order to account for the correlation among subjects within a household and control the associated type 1 error inflation, a generalized linear model will be used to estimate the odds ratio between the treatment groups by using the generalized estimation equation (GEE) approach. This model estimates a single within-household correlation coefficient.

If a subject's infection status cannot be determined due to all missing post-baseline serologic test results or RT-qPCR results during the efficacy assessment, that subject will be imputed as an event (ie, either symptomatic or asymptomatic positive SARS-CoV-2 RT-qPCR status). Additional missing data handling rules will be specified in SAP. The model will at least include the fixed category effects of treatment group (placebo versus REGN10933+REGN10987) and randomization stratification factor age (<50, ≥50 years). The model will use a compound symmetry covariance matrix and estimate the odds ratio between the treatment groups and corresponding 95% CI and p-value. If the generalized estimating equation model fails to converge due to most households containing only a single person then a logistic regression model will be used, with treatment and strata as fixed effects.

As a sensitivity analysis, subjects who develop asymptomatic or symptomatic SARS-CoV-2 infection within 72 hours of study drug dosing will be excluded. Additional sensitivity and supportive analyses will be described in the SAP.

Subgroup Analyses

Subgroups are defined by key baseline factors and listed to be considered for the comparisons between the REGN10933+REGN10987 group and placebo group in primary analysis by adding the variable of subgroup and treatment group-by-subgroup interaction term(s) to the model. The subgroups may be considered as follows:

- Age group (<50, ≥50)
- Sex
- Race
- Ethnicity
- BMI (<30, ≥30)
- Number of subjects in the same household who are infected (<2, ≥2)

Additional subgroup analyses will be defined in the SAP.

11.4.3.1.2. Primary Efficacy Analysis (Cohort B)

There are no primary efficacy endpoints in cohort B.

The key secondary endpoint in cohort B is the proportion of subjects who develop signs and symptoms (strict-term) of symptomatic SARS-CoV-2. The analysis will be performed in a similar manner as the primary endpoint in cohort A.

11.4.3.1.3. Secondary Efficacy Analyses

Secondary efficacy endpoints will be analyzed by type of endpoint for both cohort A and cohort B as follows. The analysis methods will also be applied to efficacy endpoints for exploratory endpoints in both cohort A and cohort B. For the comprehensive evaluation of efficacy, nominal p-values may be reported even if analyses of some secondary endpoints entail non-randomized comparison.

Binary Endpoints

Binary endpoints (eg, proportion of subjects with broad term symptomatic RT-qPCR confirmed infection) will be analyzed applying the same approach used for the primary efficacy in cohort A.

Continuous Endpoints

Continuous clinical endpoints (eg, number of days of symptoms) and continuous viral load endpoints (eg, maximum SARS-CoV-2 RT-qPCR $\log_{10}$ viral copies/mL in nasal swab samples) will be analyzed using the generalized linear model with GEE approach, similar to that used for the primary analysis except with the selection of an identity link function with treatment and strata as fixed effects. If the GEE model does not converge because most households are single-person households, then ANCOVA will be used.

Full details on the analyses of secondary endpoints will be provided in the SAP.

11.4.4. Control of Multiplicity

11.4.4.1. Cohort A

The overall type I error will be controlled for primary hypotheses at 2-sided test at alpha level of 0.05 as follows:

> H1: No treatment difference between REGN10933+REGN10987 and placebo in proportion of subjects who have a positive SARS-CoV-2 RT-qPCR (based on central lab testing) and signs and symptoms (strict term) of SARS-CoV-2 infection during the EAP.
>
> H2: No treatment difference between REGN10933+REGN10987 and placebo in proportion of subjects have a RT-qPCR confirmed SARS-CoV-2 infection (either asymptomatic or symptomatic) during EAP.

When 50% of subjects complete the EAP, there will be an interim analysis. To control the overall type I error at alpha level of 0.05, the alpha will be spent using the Lan-DeMets alpha spending function that approximates the O'Brien-Fleming boundary. Please see the details in Section 11.5. The Hochberg method will be applied for hypotheses H1 and H2 at 2-sided alpha level of 0.05 when all subjects in cohort A complete the EAP. If both p-values are ≤0.05, both H1 and H2 will be rejected and REGN10933+REGN10987 will be declared statistically significantly better than placebo. If 1 of the p-values is > 0.05, the other p-value will be compared with 0.025. If the smaller p-value is ≤0.025, the corresponding hypothesis will be rejected and the REGN10933+REGN10987 will be declared statistically significantly better than placebo.

If both primary efficacy endpoints are statistically significant, the alpha will be released for the key secondary endpoints.

11.4.4.2. Cohort B

The overall type I error will be controlled at alpha level of 0.05 for the formal hypothesis test as below.

> H1: No treatment difference between REGN10933+REGN10987 and placebo in proportion of subjects who subsequently develop signs and symptoms (strict term) of symptomatic SARS-CoV-2 within 14 days of a positive RT-qPCR

If the hypothesis is rejected, the full alpha will be used for the other key secondary endpoints. The details will be provided in SAP.

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The EAP is defined as the day from first dose of study drug to 28 days after the last dose of study drug.

- The Follow-up Period is defined as the end of the EAP to the end of the Follow-up Period (ie, last study visit).

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition.

TEAEs will be summarized for each of the following periods: EAP, Follow-up period, and combined across the EAP and Follow-up periods. Adverse events that occur prior to treatment will be listed.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®), version 23.0 or greater. Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

The number and percentage of subjects with TEAEs will be summarized by treatment group. Summaries will include:

- Overview of TEAEs, ie, overall number (%) of subjects with any TEAE, Serious TEAE, TEAE leading to death, or TEAE leading to study discontinuation
- TEAEs by primary SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent SAEs by primary SOC and PT
- Treatment-emergent AESIs by primary SOC and PT
- Treatment-emergent AEs leading to discontinuation by primary SOC and PT

Deaths and other SAEs will be listed and summarized by treatment group.

11.4.5.2. Other Safety (Vital Signs and Laboratory Tests)

Definitions

The following definitions will be applied to laboratory parameters and vital signs:

- The potentially clinically significant value (PCSV) criteria are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs. The PCSV criteria will be provided in the SAP.
- PCSV criteria will determine which subjects had at least 1 PCSV during the respective TEAE periods, taking into account all evaluations performed during the respective TEAE periods, including unscheduled or repeated evaluations. The number of all such subjects will be the numerator for the PCSV percentage.

<u>**Analysis**</u>

The incidence of PCSVs at any time during the TEAE period will be summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal/missing
- Abnormal according to PCSV criterion or criteria

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided for subjects meeting PCSV criteria.

11.4.5.3. Treatment Exposure

The duration of study treatment exposure will be defined as 28 days after the last dose for a subject in SAF. The follow-up period is defined as 8 months after the dose administration.

11.4.5.4. Treatment Compliance

Subject treatment compliance is not applicable for this study, since the study drug is administered once at the site and will be the same as treatment exposure.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

<u>**Dense Samples for Drug Concentration**</u>

The PK parameters to be determined for REGN10933 and REGN10987 may include, but are not limited to:

C_{max}, C_{max}/Dose, t_{max}, t_{last}, C_{last}, AUC_{inf}, AUC_{inf}/Dose, $t_{1/2}$, C_{28} (concentration in serum 28 days after dosing)

Selected PK parameters will be summarized by descriptive statistics for each cohort. All parameters will be summarized (mean, SD, %CV, range, median, and number of samples).

<u>**Sparse Samples for Drug Concentrations**</u>

The concentrations of REGN10933 and REGN109877 in serum over time will be summarized by descriptive statistics for each cohort.

No formal statistical hypothesis testing will be performed.

11.4.7. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

At a minimum, the viral-exposure response analysis will be performed. Additional exposure-response will be done for selected efficacy variables, as appropriate.

11.4.8. Analysis of Immunogenicity Data

Immunogenicity will be characterized by ADA responses and titers observed in subjects in the ADA analysis set. The ADA response categories and titer categories are defined as follows:

ADA response categories:

- ADA Negative, defined as ADA negative response in the ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, or a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when baseline results are negative or missing.
- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer categories (Maximum titer values)

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive subjects by treatment groups and ADA titer categories and at the
- Number (n) and percent (%) of treatment-boosted ADA positive subjects by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for subjects with pre-existing, treatment-emergent, and treatment-boosted ADA response.

11.5. Interim Analysis

Formal efficacy interim analyses may be conducted when 50% of subjects in cohort A complete the treatment period. Alpha will be allocated for the interim analysis using Lan-DeMets alpha-spending function that approximates the O'Brien-Fleming boundary.

For a 2-sided test, alpha-spending function has the form: $\alpha(t) = 4 * (1 - \boldsymbol{\Phi}\left(\frac{z_{\alpha/4}}{\sqrt{t}}\right))$, where $\boldsymbol{\Phi}$ denotes the standard normal cumulative function and Time t is the proportion of subjects evaluated for the primary endpoint. For example, to control the overall type I error at level of 0.05, when 50% of subjects in cohort A complete the treatment period, the $\alpha(0.5)$=0.003 will be used for primary hypotheses (ie, approximately alpha=0.049 will be used for the final analysis), where p-value in each hypothesis will be based on a 2-sided test. If both p-values are ≤0.003, both hypotheses will be rejected and REGN10933+REGN10987 will be declared statistically significantly better than placebo. If 1 of the p-values is >0.003, the other p-value is less than

0.0015, the corresponding hypothesis will be rejected and the REGN10933+REGN10987 will be declared statistically significantly better than placebo.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history/) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC)

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first subject, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of subjects are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate subject records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every subject enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each subject, the investigator must provide an electronic signature. A copy of each subject CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of subject final eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB. A copy of the IRB -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

- Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.

- Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study subjects must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the subject’s study record and a copy must be given to the subject.

13.3. Subjects Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should be identified by a subject identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The subject 's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board

An appropriately constituted IRB, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the subjects (eg, advertising) before any subject may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subject, in which case the IRB should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB should be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

A copy of the IRB approval letter with a current list of the IRB members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any subject within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of subjects required for the study are enrolled earlier than expected

In all cases, the appropriate IRB and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the subjects' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: *A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2* and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

____________________________________ __________________________

(Signature of Investigator) (Date)

____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2

Protocol Number: R10933-10987-COV-2069

Protocol Version: R10933-10987-COV-2069 Original

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00114965 v1.0

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Signature Page for VV-RIM-00114965 v1.0 Approved

Clinical Study Protocol

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2

Compound:	REGN10933+REGN10987
Clinical Phase:	3
Protocol Number:	R10933-10987-COV-2069
Protocol Version:	R10933-10987-COV-2069 Amendment 6
Amendment 6 Date of Issue:	*See appended electronic signature page*
Amendment 5 Date of Issue:	19 Jan 2021
Amendment 4 Date of Issue:	24 Nov 2020
Amendment 3 Date of Issue:	07 Oct 2020
Amendment 2 Date of Issue:	26 Aug 2020
Amendment 1 Date of Issue:	17 Jul 2020
Original Date of Issue	16 Jun 2020
Medical/Study Director:	[redacted]r, Early Clinical Development and Experimental Sciences [redacted], Early Clinical Development and Experimental Sciences [redacted], Early Clinical Development and Experimental Sciences Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 6

The primary purpose of this amendment is to revise and add objectives and endpoints, as well as to define the statistical testing hierarchy for the primary and key secondary endpoints.

Description of Change	Brief Rationale	Section(s) Changed
Objectives, Endpoints, and Planned Statistical Analysis		
The following modifications were made to the planned statistical analysis: • Revised the primary objective and endpoint for cohort A	The revision of the primary objective and endpoint for cohort A is informed by the administrative assessment of 409 cohort A seronegative subjects, where there was a 100% reduction in symptomatic events (broad-term) in the REGN10933+REGN10987 treated subjects as compared to the placebo treated subjects with 8/223 (3.6%) placebo treated subjects developing symptomatic infection versus 0/186 (0%) REGN10933+REGN10987 treated subjects; OR 0.00 (0.00, 0.69) p<0.01. The single primary objective is now to evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR	Clinical Study Protocol Synopsis: Objectives, Endpoints, Statistical Plan Section 2 Study Objectives Section 2.1.1.1 Cohort A Primary Efficacy Objective Section 4 Endpoints Section 4.1.1 Cohort A Primary Endpoints Section 6.1.6 Description of Study Cohorts Section 9.2.2.2 COVID-19 Symptomology (Strict Terms, Broad Terms, and CDC Definition)
• Added a primary objective and endpoint for cohort B	Because cohort B is a separate population from cohort A, where cohort B subjects are infected at baseline (SARS-CoV-2 RT-qPCR positive), a new primary objective and endpoint was added to evaluate whether REGN10933+REGN10987 may be efficacious as preemptive therapy to prevent symptoms in those who are already infected, therefore the objective is to evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing COVID-19 symptoms (broad-term) in asymptomatic subjects that are SARS-CoV-2 RT-qPCR positive and seronegative at baseline	Section 2.2 Cohort B and Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline Section 2.2.1 Cohort B Primary Efficacy Objective Section 2.2.2 Cohort B and Cohort B1 Primary Safety Objective Section 4.2.1 Cohort B Primary Efficacy Endpoint
Defined key secondary endpoints for all cohorts	The revision of the key secondary objectives and endpoints is informed by the administrative assessment of 409 cohort A seronegative subjects, such that revised key secondary endpoints now include the evaluation of REGN10933+REGN10987 as compared to placebo to reduce high viral load, defined as viral load >4 ($\log_{10}$ copies/mL), duration of symptomatic infection, duration of high viral load infection, duration of any infection, development of infection (regardless of symptoms), all during the 28 day efficacy	Section 4.1.2 Cohort A Key Secondary Endpoints Section 4.2.2 Cohort B Key Secondary Endpoints

	assessment period. An additional key secondary endpoint links the Regeneron R10933-10987-COV-2067 outpatient treatment study with the R10933-10987-COV-2069 prevention study, where households who enrolled symptomatic infected household members into 2067 and their asymptomatic uninfected members into 2069. These data may inform whether treatment of symptomatic infected household members with REGN10933+REGN10987 may prevent infection in uninfected household members.	
• Revised the secondary and exploratory objectives and endpoints for all cohorts	Objectives and endpoints that were determined not to be key are listed as other secondary and exploratory.	Section 2.1.3 Cohort A and Cohort A1 Secondary Objectives Section 2.1.4 Cohort A and Cohort A1 Exploratory Objectives Section 4.1.3 Cohort A and Cohort A1 Other Secondary Endpoints Section 4.1.4 Cohort A and Cohort A1 Exploratory Endpoints Section 2.2.3 Cohort B and Cohort B1 Secondary Objectives Section 2.2.4 Cohort B and Cohort B1 Exploratory Objectives Section 4.2.3 Cohort B and Cohort B1 Other Secondary Efficacy Endpoints Section 4.2.4 Cohort B and Cohort B1 Exploratory Endpoints
• Updated the statistical hypotheses and the planned analyses for efficacy and safety	Statistical hypothesis and planned analyses were updated in accordance with the revised primary(s) and key secondary objectives and endpoints	Section 11.1 Statistical Hypothesis Section 11.4 Statistical Methods Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.1.1. Sensitivity Analyses Section 11.4.3.1.2. Subgroup Analyses Section 11.4.3.2. Key Secondary Efficacy Analyses Section 11.4.3.3. Other Secondary Efficacy Analyses Section 11.4.1 Subject Disposition Section 11.4.5.1. Adverse Events

• The scope of analyses for first-step and second-step analyses were specified. • The data-cutoff for the first step analysis was specified	The rationale for scope of analyses and the first-step analysis data cut off are based on the results of the administrative assessment and the sample size justification.	Section 11.4.9. Timing of Statistical Analysis
• Defined the statistical testing hierarchy for the primary endpoint and key secondary endpoints for cohort A and cohort B	The statistical testing hierarchy was determined by considering which endpoints would be most relevant and important to understand the efficacy of REGN10933+REGN10987 to prevent symptomatic infection and transmission potential, including the prevention of infections with high viral loads, longer duration of high viral loads, and whether REGN10933+REGN10987 can be considered for treatment of the symptomatic infected household member to prevent infection of the uninfected household member.	Section 11.4.4. Control of Multiplicity Table 10 Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-A Table 11 Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-B
• Updated the sample size justification	Based on the decision not to conduct any interim analysis, the full alpha will be used for the first-step analysis.	Section 11.2 Justification of Sample Size Table 9 Simulated Power for Household Design (1248 Subjects over 430 Households Section 11.2.1 Cohort A: Adult and Adolescent Subjects (≥12 years) Who Are SARS-CoV-2 RT-qPCR Negative at Baseline Section 11.2.2 Cohort B: Adult and Adolescent Subjects (≥12 years) Who Are SARS-CoV-2 RT-qPCR Positive at Baseline
• Updated the analysis set definitions	The definitions were revised to specify that only seronegative subjects are eligible for the efficacy analysis sets.	Section 11.3.1 Efficacy Analysis Sets Section 11.3.2 Safety Analysis Set Section 11.3.4 Immunogenicity Analysis Set Section 11.3.5 Neutralizing Antibody Analysis Set
• Added statement that no interim analysis will be conducted for this study	No interim analyses will be conducted for this study.	Section 8.5 Blinding Section 11.5 Interim Analysis
• Updated the variable definition for SARS-CoV-2 infection	The definition for positive and negative infection results was revised for consistency with the statistical analyses specified.	Section 5.2 Efficacy Variables
Clinical Rationales for the Changes to Objectives and Endpoints		
• Provided the rationales for the changes to the objectives and endpoints	The rationales for the primary and secondary objectives and endpoints were revised based on the results of the administrative assessment .	Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 3.2.5 Primary Objective

		Section 3.2.6 Secondary Objectives
Study Design		
• Added collection of external SARS-CoV-2 test results for subjects with COVID-19 symptoms	Collection of local SARS-CoV-2 test results will support confirmation of infection in subjects with COVID-19 symptoms	Section 6.1.4 Efficacy Assessment Period Section 6.1.5 Follow-up Period Section 8.8 Concomitant Medications and Procedures Section 9.1.1 Schedule of Events Table 3 (Cohorts A and B [Adult /Adolescent Subjects], RT qPCR-Negative and Positive) Footnotes), footnote #9 Section 11.4.3.1 Primary Efficacy Analysis
Other changes		
• Updated confidentiality statement	Revised per current corporate version	Title Page
• Minor editorial updates -changed verb tense -fixed numbered list formatting	Corrected minor issues.	Throughout the document

Amendment 5

The primary purpose of this amendment is to describe the verification of the sample size assumptions used to design the study.

Description of Change	**Brief Rationale**	**Section(s) Changed**
• Added an administrative assessment for assumption verification and sample size estimation for the study • Sample size increased to 3500 subjects to ensure that the formal analysis of the phase 3 study has an adequate sample size.	The initial sample size assumptions used for the study design were based on COVID-19 household contact infection rates observed in the literature available during study planning. Currently, the range of reported infection rates, including onset of infection and symptomatic infection, is more variable in the literature than originally understood. Some early study data will be used, therefore, to verify the assumptions and estimated sample size by assessing infection rates in the population in this study.	Clinical Study Protocol Synopsis: Study Design, Population, Statistical Plan Section 3.2.2 Subject Population Section 6.1 Study Description and Duration Section 7.1 Number of Subject Planned Section 11.2 Justification of Sample Size Section 11.2.1 Cohort A- SARS-CoV-2 RT-qPCR Negative Section 8.5 Blinding Section 11.3.1 Full Analysis Sets Section 11.4.9 Timing of Statistical Analysis
• Consolidated the dose information into a single section of the protocol	The dose information is presented in one section.	Section 8.1 Investigational and Reference Treatments Section 8.4 Method of Treatment Assignment
• Added guidance related to the use of an EUA approved COVID-19 vaccine by subjects in the study	Specified that an EUA approved COVID-19 vaccine is prohibited during the EAP and permitted in the Follow-up period. The unblinding performed for the purpose of COVID-19 vaccine decision making does not need to be discussed with the medical director.	Section 8.6 Emergency Unblinding Section 8.9 Prohibited Medications Section 8.10 Permitted Medications
• Added collection of information for the household members related to an EUA approved monoclonal antibody treatment for COVID-19 or participation in the R10933-10987-COV-2067 study	Collection of this information is needed to understand the COVID-19 transmission in the household setting.	Section 9.1.1 Schedule of Events Table 3 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes, #16 Section 9.1.3 f Schedule of Events Table 5 Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Footnotes, # 15 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit
• Updated the title for medical/study directors	The medical/study director title were updated	Title page

Amendment 4

The primary purposes of this amendment are 1) to change from 2 primary endpoints to 1 primary endpoint, 2) to increase the sample size, 3) to allow for the inclusion of pediatric subjects aged <12 years, 4) to allow for the inclusion of women who are pregnant or breastfeeding, and 5) to add an exploratory objective and endpoint to assess whether the treatment of index cases with REGN10933+REGN10987 in the R10933-10987-COV-2067 study has an impact on rates of infectivity in household contacts in this study. The endpoint and sample size changes are based on blinded review of the data with regard to SARS-CoV-2 infection events and baseline seropositivity prevalence in cohort A. The inclusion of pediatric subjects younger than 12 years and pregnant or breastfeeding women is considered relevant to the populations at risk for infection with SARS-CoV-2.

Description of Change	Brief Rationale	Section(s) Changed
• Study now has 1 primary efficacy endpoint: proportion of SARS-CoV-2 infection during the efficacy assessment period (EAP). The proportion of "strict-term" symptomatic SARS-CoV-2 infection during the EAP has been moved to a secondary endpoint.	A blinded analysis of approximately 25% of enrolled subjects was performed, demonstrating that lower than expected symptomatic infection events were observed in Cohort A: adult and adolescent Subjects (≥12 years) who are SARS-CoV-2 RT-qPCR Negative at Baseline. If 2 primary endpoints were to be retained, the study is considered infeasible as the sample size would need to increase several fold to have enough symptomatic events in cohort A to be powered sufficiently. The single primary endpoint of the prevention of laboratory confirmed SARS-CoV-2 infection is considered highly clinically important because infection is the necessary antecedent event for illness.	Clinical Study Protocol Synopsis: Primary Endpoints, Secondary Endpoints, Statistical Plan Section 3.2.5 Primary Objectives Section 3.2.6 Secondary Objectives Section 4.1.1 Cohort A Primary Endpoints Section 4.1.2 Cohort A and Cohort A1 Secondary Endpoints Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.4.1 Cohort A
• Increased the sample size for the study	A blinded analysis of approximately 25% of enrolled subjects was performed, demonstrating a higher than expected seropositivity rate at baseline in Cohort A. The sample size of cohort A is therefore being revised upwards to account for this seropositivity rate because only seronegative individuals are included in the primary analysis population.	Section 7.1 Number of Subjects Planned Section 11.2 Justification of Sample Size Section 11.2.1 Cohort A- SARS-CoV-2 RT-qPCR Negative Section 11.2.2 Cohort B - SARS-CoV-2 RT-qPCR Positive
• Pediatric subjects aged <12 years are added to the study. • Added description of the informed consent for the parent/guardian and assent for pediatric subjects	Pediatric subjects <12 years of age are added to the study because they are a population at risk of SARS-COV-2 infection in a household and may contribute to the infection of others in the household. Pregnant women who are household contacts of an index case are at risk of SARS-CoV-2 infection and are at higher	Clinical Study Protocol Synopsis: Objectives, Study Design, Sample Size, Target Population, Treatments, Primary Endpoints, Secondary Endpoints, Procedures and Assessments, Statistical Plan Section 1.2 Populations at Increased Risk of SARS-CoV-2 Infection Among Household Contacts of a Person Infected with SARS-CoV-2

• Pregnant women and breastfeeding women are added to the study. • The requirement for contraception use by women of childbearing potential (WOCBP) was removed • The requirement for contraception use by men enrolled in the study was removed. • The stratification for pediatric subjects in randomization will take weight group into account (ie, ≥20 kg, ≥10 kg to <20 kg, and <10 kg).	risk of severe COVID-19 than non-pregnant women. Inclusion of pediatric subjects, pregnant women, and breastfeeding women is supported by ongoing blinded review of the safety profile in adult and adolescent subjects, which is demonstrating that REGN10933+REGN10987 treatment is sufficiently well-tolerated. In addition, there is no human fetal tissue cross-reactivity of REGN10933 and REGN10987 to suggest a risk to the fetus. The safety profile in pediatric subjects less than 12 years and pregnant and breastfeeding women is expected to be similar to that observed in adults and adolescents. Because pregnant women are allowed in the study, contraception for women of childbearing potential (WOCBP) is no longer required as an exclusion criterion. However, WOCBP will undergo pregnancy testing prior to dosing and at the end of study. Women who are pregnant or who become pregnant during the study will be followed for the outcome of their pregnancy. The inclusion of pregnant women who are identified at study entry as well as women who become pregnant during the study will provide important safety and efficacy data in this population at increased risk of severe COVID-19. Because pregnant women are allowed in the study, contraception for men enrolled in the study is no longer required as an exclusion criterion. Information regarding pregnancies occurring in the female partners of male study subjects will not be solicited as the risk of exposure is negligible in this scenario The stratification is to ensure relative balance in treatment allocation among different pediatric weight groups for PK analysis.	Section 1.5 A Randomized, Placebo-Controlled Study of Anti- Spike Protein Monoclonal Antibodies as Post-Exposure Prophylaxis and Pre-emptive Therapy in Household Contacts Section 3.2.1 Study Design Section 3.2.2 Subject Population Section 3.2.4 Sentinel Safety Group and Subsequent Safety Reviews Section 3.3 Risk-Benefit Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 6.1.2 Pediatric Subjects (<12 years) Section 6.1.3 Screening/Baseline Section 7.1 Number of Subjects Planned Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, criterion #1 Section 7.2.2 Exclusion Criteria, #14, #15, #16 Section 8.6 Emergency Unblinding Section 13.2 Informed Consent
• Specified doses for subjects <12 years of age using weight-tiered dosing groups	Based on population pharmacokinetics modeling and simulation, lower doses were selected for children using a weight-tiered approach in order to achieve approximately	Section 3.2.7 Rationale for Dose Selection Figure 1 Study Flow Diagram

	similar exposures as those observed in adults. Weight is the primary variable influencing drug exposure.	Section 8.1 Investigational and Reference Treatments Section 8.4 Method of Treatment Assignment Section 9.2.4 Drug Concentration and Measurements Table 6 Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.1.4 Schedule of Events Table 6 Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing
• Subjects <12 years of age will be divided into 2 independent study cohorts, cohort A1 (SARS-CoV-2 RT-PCR negative at baseline) or cohort B1 (SARS-CoV-2 RT-PCR positive at baseline) using the same parameters used to define cohort A and B for the adult and adolescent subjects. • Study objectives and endpoints were specified for cohort A1 and cohort B1 • Cohort A1 and cohort B1 will be analyzed separately from the adult and adolescent subjects.	The pediatric subjects <12 years are proposed to be analyzed separately from the adults and adolescents because 1) drug concentrations and exposures need to be evaluated and may change during the study, 2) nasopharyngeal (NP) sampling for RT-qPCR is not identical to that used for adult and adolescent subjects, 3) subjects <12 years may have milder disease, 4) COVID-19 signs and symptoms/AE reporting may be different in subjects <12 years	Clinical Study Protocol Synopsis: Objectives, Sample Size, Target Population, Treatments, Primary Endpoints, Secondary Endpoints, Statistical Plan Section 2 Study Objectives Section 2.1 Cohort A: SARS-CoV-2 RT qPCR Negative at Baseline Section 2.1.2 Cohort A and Cohort A1 Primary Safety Objective Section 2.1.3 Cohort A and Cohort A1 Secondary Objectives Section 2.1.4 Additional Cohort A1 Secondary Efficacy Objective Section 2.1.5 Cohort A and Cohort A1 Exploratory Objectives Section 2.2 Cohort B and Cohort B1: SARS-CoV-2 RT qPCR Positive at Baseline Section 2.2.1 Cohort B and Cohort B1 Secondary Objectives Section 2.2.2 Cohort B and Cohort B1 Exploratory Objectives Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 4.1 Cohort A and Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline Section 4.1.1 Cohort A Primary Endpoints

		Section 4.1.2 Cohort A and Cohort A1 Secondary Endpoints Section 4.1.3 Cohort A and Cohort A1 Exploratory Endpoints Section 4.2 Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline Section 4.2.1 Cohort B and Cohort B1 Secondary Efficacy Endpoints Section 4.2.2 Cohort B and Cohort B1 Exploratory Endpoints Section 6.1.6 Description of Study Cohorts Section 11.3.1 Full Analysis Sets Section 11.4.3.2 Secondary Efficacy Analyses Section 11.4.5.1 Adverse Events
• Specified assessments for cohort A1 and cohort B1 (subjects <12 years of age)	The assessments were modified for pediatric subjects younger than 12 years to minimize blood draws and procedures.	Clinical Study Protocol Synopsis: Procedures and Assessments Table 3 Schedule of Events (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 2 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes #2, #4, #6, #12, #18, #19, #20 Table 4 Schedule of Events: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.1.2 Schedule of Events Table 3: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentrations, Immunogenicity, and Laboratory Testing Table 5 Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Section 9.1.3 Schedule of Events Table 4 Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Footnotes Table 6 Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing

		Section 9.1.4 Schedule of Events Table 5: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.2.2.1 Nasopharyngeal Swab SARS-CoV-2 RT-qPCR Test (Central Lab) Section 9.2.2.2 COVID-19 Symptomology (Strict Terms, Broad Terms, and CDC Definition) Section 9.2.2.3 Assessment of Medically Attended Visits Section 9.2.2.4 Absenteeism Assessment Section 9.2.3.1Targeted Physical Examination and Vital Signs Section 9.2.3.2 Laboratory Testing Section 9.2.6 Exploratory Pharmacodynamic/Biomarker Procedures Section 9.2.7 Pharmacogenomic Analysis (Optional) Section 10.1.3 Events that Require Expedited Reporting to Sponsor
• Added exploratory objective to assess the impact of the treatment of index cases receiving REGN10933+REGN10987 in study R10933-10987-COV-2067 on rates of infectivity in household contacts	Included to study the infection dynamics within a household and assess if the treatment of the index case with REGN10933+REGN10987 in study R10933-10987-COV-2067 affects secondary infection rates in study R10933-10987-COV-2069.	Section 2.1.5Cohort A and Cohort A1 Exploratory Objectives Section 4.1.3Cohort A and Cohort A1 Exploratory Endpoints Section 9.1.1Schedule of Events Table 2 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnote #16
• Added a secondary objective and an endpoint based on the CDC definition of COVID-19 symptoms	The use of the CDC definition for a secondary objective and an endpoint support comparability of results across clinical studies in the field.	Clinical Study Protocol Synopsis: Objectives, Endpoints, Secondary Endpoints, Procedures and Assessments, Statistical Plan Section 2.1.3 Cohort A and Cohort A1 Secondary Objectives Section 2.2.1 Cohort B and Cohort B1 Secondary Objectives Section 3.2.6 Secondary Objectives Section 4.1.2 Cohort A and Cohort A1 Secondary Endpoints Section 4.1.3 Cohort A and Cohort A1 Exploratory Endpoints Section 4.2.1 Cohort B and Cohort B1 Secondary Efficacy Endpoints

		Section 4.2.2 Cohort B and Cohort B1 Exploratory Endpoints Section 5.2 Efficacy Variables Section 9.2.2.2 COVID-19 Symptomology (Strict Terms, Broad Terms, and CDC Definition) Table 7 Strict-Terms ,and Broad-Terms, and CDC Definition COVID-19 Signs and Symptoms
• Changed the definition of the index case such that the index case must be the first household member known to be infected with SARS-CoV-2	Adding the requirement that the index case be the first known infected household member in the house may increase the number of household members who have not yet been exposed to SARS-CoV-2 and may therefore still be susceptible to infection.	Clinical Study Protocol Synopsis: Study Design, Target Population Section 2 Study Objectives Section 3.2.1 Study Design Section 3.2.2 Subject Population Section 6.1 Study Description and Duration Section 6.1.6 Description of Study Cohorts Section 7.2 Study Population Section 7.2.2 Exclusion Criteria, #2
• Revised the description of the screening and baseline visit to allow a remote visit to occur on the day prior to randomization and study drug administration to sign the informed consent form and collect medical history and concomitant medication use.	Provide flexibility for subjects to complete the screening remotely so that in-person screening may be abbreviated due to COVID-19 considerations	Section 6.1 Study Description and Duration Section 9.1.1 Schedule of Events Table 2 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes #1
• Added assessment of neutralizing antibodies, if feasible	Provide information about the assessment of NAbs in the study	Clinical Study Protocol Synopsis: Secondary Endpoints Section 3.2.1 Study Design Section 4.1.2 Cohort A and Cohort A1 Secondary Endpoints Section 4.2.2 Cohort B and Cohort B1 Exploratory Endpoints Section 5.5 Immunogenicity Variables Section 9.1.2 Schedule of Events Table 3: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentrations, Immunogenicity, and Laboratory Testing Section 9.1.4 Schedule of Events Table 5: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.2.5 Immunogenicity Measurements and Samples

		Section 11.3.4 Immunogenicity Analysis Sets Section 11.4.8 Analysis of Immunogenicity Data
• Added a description of current approved treatment and therapies for COVID-19	Provide information about current treatments and therapies for COVID-19	Section 1.5 A Randomized, Placebo-Controlled Study of Anti- Spike Protein Monoclonal Antibodies as Post-Exposure Prophylaxis and Pre-emptive Therapy in Household Contacts
• Clarified the exclusion of drugs used to treat COVID-19	Specified that prohibited drugs (eg, hydroxychloroquine) can be used to treat a non-COVID-19 disease (eg, autoimmune disease).	Section 7.2.2 Exclusion Criteria, #2, #12 Section 8.9 Prohibited Medications
• Minor editorial updates -added abbreviations -changed verb tense - added and deleted references	Updated the abbreviation and reference lists.	Throughout the document

Amendment 3

The primary purpose of this amendment is to include adolescent subjects aged 12 years to less than 18 years in the study. The inclusion of adolescent subjects is considered relevant to the populations at risk for infection with SARS-CoV-2.

Description of Change	**Brief Rationale**	**Section(s) Changed**
• Adolescent subjects aged 12 years to less than 18 years are added to the study • Provided a rationale for dose selection for adolescent subjects (≥40 kg) • Revised the description of women of childbearing potential (WOCBP) to include 'girls at or beyond menarche (≥12 to <18 years of age)' • Added description of the informed consent process	Adolescent subjects ≥12 to <18 years of age (weight ≥40 kg) are added to the study because they are a population at risk of SARS-CoV-2 infection in a household. Inclusion of adolescent subjects is supported by ongoing blinded review of the safety profile, which is demonstrating that REGN10933+REGN10987 treatment is well-tolerated in more than 1000 adult subjects who have received drug. Defined the age range for adolescent female subjects to be considered WOCBP.	Clinical Study Protocol Synopsis: Study Design, Population, Treatments, Procedures and Assessments, Statistical Plan Section 1.2 Populations at Increased Risk of SARS-CoV-2 Infection Among Household Contacts of a Person Infected with SARS-CoV-2 Section 2 Study Objectives Section 3.2.1 Study Design Section 3.2.2 Subject Population Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 3.2.4 Sentinel Safety Group and Subsequent Safety Reviews Section 3.2.5 Primary Objectives Section 3.2.6 Rationale for Dose Selection Section 3.3 Risk-Benefit Section 6.1 Study Description and Duration

for adolescent subjects and their parent/guardian • The stratification for age group in randomization will take adolescents into account (ie, ≥12 to <18, ≥18 to <50, ≥50). • Specify the sample size re-estimation will be conducted periodically, starting when approximately 25% of subjects in cohort A have completed the efficacy assessment period (EAP). • Summaries of treatment-emergent adverse events (TEAEs) for adolescent subjects will also be provided.	Provided instruction for documenting consent of the adolescent subject and their parent/guardian The stratification is to ensure relative balance in treatment allocation in adolescents. The rate of symptomatic SARS-CoV-2 infections among adolescent subjects may differ from adults. Since adolescent subjects are being added after the start of the study, greater flexibility in the timing of the sample size re-estimations is needed to ensure that the attack rate can be estimated for adolescent subjects. To evaluate the safety data among adolescent subjects.	Section 6.1.1 Sentinel Subjects and Staggered Enrollment/Dosing Section 6.1.2 Screening/Baseline Section 6.1.3 Efficacy Assessment Period Section 6.1.4 Follow-up Period Section 6.1.5 . Description of Study Cohorts Section 6.3.2 Safety Review Committee for REGN 2069/CoVPN3502 Section 7.1 Number of Subjects Planned Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, criterion #1 Section 7.2.2 Exclusion Criteria, #16 Section 7.3 Premature Withdrawal from the Study Table 1 Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts[Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes #2, #4, #6, #12, #19 Section 9.2.1.1 Informed Consent Section 9.2.2.2 COVID-19 Symptomology (Strict Terms and Broad Terms) Section 9.2.3.1 Targeted Physical Examination and Vital Signs Section 9.2.4 Drug Concentration and Measurements Section 10.1.1 General Guidelines Section 11.2.1 Cohort A- Justification of Sample Size Section 11.4.5.1 Adverse Events Section 13.2 Informed Consent
• Added description that the investigator will recommend that subjects measure their body temperature daily and when they feel unwell. • Revised the description of subject subset 1 and subset 2 to indicate these are completed.	Per protocol, fever is 1 of the signs that define 1 of the primary endpoints of the study (ie, symptomatic SARS-CoV-2 infection). In order to reduce the possibility that study subjects forget to measure their temperature, wording was added to the protocol for investigators to recommend that temperature be measured daily and when subjects feel unwell These subject subsets are completed	Clinical Study Protocol Synopsis: Study Design, Statistical Plan Section 6.1.3 Efficacy Assessment Period Section 6.1.4 Follow-up Period Table 2 Schedule of Events for Drug Concentration, Immunogenicity, and Laboratory Testing Section 10.1.1 General Guidelines Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A) Section 11.4.3.1.3 Secondary Efficacy Analyses

• Revised the description of the automated reminders to being optional if not technically feasible (language barriers, no mobile phone, etc) • Modify the analysis for continuous endpoints from GEE model to ANOVA/ANCOVA model.	The use of automated reminders was made optional in case of technical/operational difficulties/delays in implementation. For continuous endpoints the analysis population consists of those subjects who have at least 1 positive RT-qPCR during EAP instead of all subjects in full analysis set (FAS) (ie, smaller sample size). Thus, the ANOVA model will be used and for change and percent change from baseline endpoints the relevant baseline values will be included as covariate in the model (ie, ANCOVA model).	
• Minor editorial updates -added a statement about anti-drug antibody (ADA) assessment to the synopsis - deleted 'post-baseline' -added and deleted references	Added for consistency with the protocol body Corrected an error Updated the reference list	Clinical Study Protocol Synopsis: Procedures and Assessments Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 19 References

Amendment 2

The primary purpose of this amendment is to remove the requirement for subjects to have at least 48 hours of sustained exposure to the index case. The 48-hour exposure requirement is considered to be too restrictive and not necessary since the subject is expected to be living in the same household with the index case. Additionally, the definition of 'household' was updated to clarify the specific characteristics of a household; the guidance for the conduct of the local diagnostic assay testing at baseline was revised; and the analysis of cohort B was revised to include all subjects at baseline (ie, subjects who are seropositive or seronegative).

Description of Change	**Brief Rationale**	**Section(s) Changed**
• Removed requirement for subjects to have sustained exposure to the index case for 'at least 48 hours'	The 48-hour exposure requirement is considered to be too restrictive and not necessary since the subject is expected to be living in the same household with the index case. These changes were made to address feasibility issues.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, criterion #2
• Updated the definition of 'household' with specific characteristics.	This change was made to specify the characteristics of a 'household 'that are compatible with the	Section 3.2.2 Subject Population

	assumptions used for the sample size calculation.	
• Revised the description of local diagnostic assay to include SARS-CoV-2 antigen or RT-PCR using an appropriate sample such as nasopharyngeal (NP), nasal, oropharyngeal (OP), or saliva. • Added the option to not perform the local diagnostic assay for SARS-CoV-2 if the results are not anticipated to be available in a timely manner for randomization. • Revised the description of the automated reminders to be 'implemented as soon as technologically feasible' • Revised the Schedule of Events and footnotes to clarify the procedures for subjects who are RT-qPCR negative and the procedures for subjects who are RT-qPCR positive	These changes were made to address feasibility and operational constraints for clinical sites.	Clinical Study Protocol Synopsis, Study Design, Procedures and Assessments Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 5.1 Demographic and Baseline Characteristics Figure 1 Study Flow Diagram Section 6.1 Study Description and Duration Section 6.1.2 Screening/Baseline Section 6.1.3 Efficacy Assessment Period Section 8.4 Method of Treatment Assignment Table 1 Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes - #7, #9, #17, #18, #19, #20 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 9.2.1.2 Local Diagnostic Assay for SARS-CoV-2
• Revised the planned analysis for cohort B to also include subjects who are seropositive at baseline • Updated the cohort B exploratory endpoints • Updated the primary efficacy analysis (cohort A) and secondary efficacy analyses	This change was made since many of the subjects enrolled in cohort B (RT-qPCR positive at baseline) are seropositive at baseline, using semi-quantitative assays, and the presence of antibodies in subjects with an active infection is of unknown clinical relevance.	Clinical Study Protocol Synopsis: Objectives, Endpoints, Statistical Plan Section 2 Study Objectives Section 2.1 Cohort A: SARS-CoV-2 RT qPCR Negative at Baseline Section 2.2 Cohort B: SARS-CoV-2 RT qPCR Positive at Baseline Section 2.2.1 Cohort B Secondary Objectives Section 2.2.2 Cohort B Exploratory Objectives Section 4.1 Cohort A: SARS-CoV-2 RT qPCR Negative at Baseline Section 4.2 SARS-CoV-2 RT-qPCR Positive at Baseline Section 4.2.1 Cohort B Secondary Efficacy Endpoints Section 4.2.2 Cohort B Exploratory Endpoints Section 11.3.1 Full Analysis Sets

		Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A) Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A) Section 11.4.3.1.2 Events that Require Expedited Reporting to Sponsor Section 11.4.3.1.3 Secondary Efficacy Analyses
• Added the caveat that the use of automated reminders for subjects would be implemented if systems allow, as soon as or if feasible.	This change was made to clarify the use of automated reminders in the study.	Section 6.1.3 Efficacy Assessment Period
• Added a summary of safety results from the sentinel safety group of this study	This summary was added to present the safety results.	Section 3.2.1 Study Design
• Revised the description of the Safety Review Committee	Clarified the composition of the Safety Review Committee	Section 6.3.2 Safety Review Committee for REGN 2069/CoVPN3502
• Removed 'electrocardiogram' from the description of results of the sentinel safety group data from earlier studies in the REGN10933+REGN10987 clinical development program	This change is a correction of an error in the description of the assessments for the sentinel safety group.	List of Abbreviations Section 3.2.4 Sentinel Safety Group and Subsequent Safety Reviews Section 3.3 Risk-Benefit
• Revised text describing the measurement and analysis of drug or anti-drug antibodies (ADA) • Updated the footnotes describing the collection of PK and ADA samples	These changes clarify the descriptions related to PK or ADA assessments.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Cohort A Secondary Endpoints Section 5.4 Pharmacokinetic Variables Table 2 Schedule of Events for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.1.2 Schedule of Events Table 2: Drug Concentrations, Immunogenicity, and Laboratory Testing, Footnotes #6, #7 Section 11.3.3 Pharmacokinetic Analysis Set Section 11.3.4 Immunogenicity Analysis Set
• Added the statement highlighting that for this study only severity grade 3 or above for anaphylaxis, allergic reaction (hypersensitivity reaction), and injection site reaction are reportable as	This change was made to clarify the reporting of AESIs.	Table 4 NCI-CTCAE Severity Grading System for Adverse Events for Anaphylaxis, Allergic Reaction, and Injection Site Reaction

adverse events of special interest (AESIs)		
• Minor editorial update - addition of EudraCT number to the title page - corrected a sentence in the Introduction - minor edits for clarity - study monitoring section updated to match the current protocol template - Risk Management Lead updated to Global Safety Lead to match current nomenclature for role	Throughout	Title Page Section 1.3 The Role of Spike Protein in SARS-CoV-2 Pathogenesis Section 5.2 Efficacy Variables Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS0CoV-2 Infection Section 6.1.1 Sentinel Subjects and Staggered Enrollment/Dosing Section 6.3.2 Safety Review Committee for REGN 2069/CoVPN3502 Section 12.2.1 Monitoring of Study Sites

Amendment 1

The purpose of this amendment is to change the collection of respiratory samples for SARS-CoV-2 reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) from nasal swabs and saliva samples to nasopharyngeal (NP) swab samples due to analysis of data from baseline samples from the REGN10933+REGN10987 treatment studies, where study patients were sampled by NP swabs, nasal swabs, and saliva for side-by-side comparison. NP swabs had markedly better sensitivity to detect SARS-CoV-2 than nasal swabs and saliva samples. Additionally, the requirement for local serology testing at baseline was removed because it is anticipated that most subjects will be negative and local serology testing is not feasible at many sites. In addition, this amendment includes updates to address health authority feedback and collaborator comments.

Description of Change	**Brief Rationale**	**Section(s) Changed**
• Changed collection from nasal swabs and saliva samples to nasopharyngeal (NP) swabs for SARS-CoV-2 RT-qPCR test • Removed collection of nasal swab and saliva samples for SARS-CoV-2 RT-qPCR test • Removed endpoints based on analysis of saliva samples for SARS-CoV-2 RT-qPCR test • Clarified that molecular diagnostic RT-PCR tests, qualitative and quantitative, will be unblinded to site personnel and the Sponsor	Based on review of blinded RT-PCR data from REGN10933-10987 treatment studies, use of NP swab samples had better sensitivity to detect RT-PCR positivity than nasal swab and saliva samples. This change is to ensure proper medical care and isolation of positive subjects and to ensure appropriate quality control of NP samples.	Clinical Study Protocol Synopsis: Study Design, Endpoints, Procedures and Assessments, Statistical Plan Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 3.2.5 Primary Objectives Section 4.1.2 Cohort A Secondary Endpoints Section 4.1.3 Cohort A Exploratory Endpoints Section 4.2.1 Cohort B Secondary Endpoints Section 4.2.2 Cohort B Exploratory Endpoints Section 5.2 Efficacy Variables Figure 1 Study Flow Diagram Section 6.1.3 Screening/Baseline Section 6.1.4 Efficacy Assessment Period Section 6.1.5 Follow-up Period Table 3 Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes - #4, #7, #9

		Section 9.2.2.1 Nasopharyngeal Swab SARS-CoV-2 RT-qPCR Test (Central Lab) Section 9.2.2.2 COVID-19 Symptomology (Strict Terms and Broad Terms) Section 9.2.6.1.1 Viral Sequencing Section 9.2.6.2 Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies Section 11.4.1 Subject Disposition Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A) Section 11.4.3.2 Secondary Efficacy Analyses Section 11.4.4.1 Cohort A Section 11.4.4.2 Cohort B Section 11.4.5.1 Adverse Events Section 11.4.5.2 Other Safety (Vital Signs and Laboratory Tests Section 11.4.6.1 Analysis of Drug Concentration Data Section 11.4.7 Pharmacokinetics and Pharmacokinetics /Pharmacodynamics Section 11.5 Interim Analysis
• Removed collection of local serology (onsite) at baseline	The purpose of including local serology testing as a stratification factor for randomization was to improve the relative balance of enrollment of seronegative and seropositive subjects in each of the study arms. However, due to clinical laboratory restrictions, local testing using the lateral flow immunoassay is not feasible at most sites. Additionally, the majority of subjects are expected to be seronegative. Because serology testing will be performed by the central lab, subgroup analyses will be performed using baseline central lab serology data and this analysis will not be affected by the elimination of local serology testing.	Clinical Study Protocol Synopsis: Study Design Section 2 Objectives Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 5.1 Demographic and Baseline Characteristics Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 6.1.3 Screening/Baseline Section 8.4 Method of Treatment Assignment Section 8.5 Blinding Table 3 Schedule of Events (All Cohorts, RT qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes - Footnote #8 (removed) Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit
• Removed mention of the sentinel group from the study REGN10933-10987-COV-2068	The REGN10933-10987-COV-2068 study was not initiated in parallel with 2069;	Figure 1 Study Flow Diagram

	therefore, the sentinel group is based on REGN10933-10987-COV-2069 study only.	Section 6.1.1 Sentinel Subjects and Staggered Enrollment/Dosing
• Specify that index case test results can be from SARS-CoV-2 diagnostic test formats that are approved or have Emergency Use Authorization issued by the US FDA or by local health authority.	To improve the feasibility of enrolling household contacts due to the short window (96 hours) between the collection of the index cases' positive SARS-COV-2 RTPCR diagnostic test sample.	Clinical Study Protocol Synopsis: Study Design, Population Section 3.2.1 Study Design Section 3.2.2 Subject Population Section 6.1 Study Description and Duration Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, criterion #2
• Revised the description of the use of any unused or leftover biological samples collected during the study for exploratory research to indicate that the maximum time period of allowable storage (for both exploratory research samples and pharmacogenomic samples) may be shorter per regional laws and regulations	To clarify the intended use and storage of biological samples collected.	Section 9.2.4 Drug Concentration and Measurements Section 9.2.5 Immunogenicity Measurements and Samples Section 9.2.6 Exploratory Pharmacodynamic/Biomarker Procedures Section 9.2.6.2 Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies Section 9.2.7 Pharmacogenomic Analysis (Optional)
• Clarify the imputation method for missing RT-qPCR results	revised the rules for imputing results	Clinical Study Protocol Synopsis: Statistical Plan Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A)
• Added country as a fixed factor in the statistical model • Added a description of the timing of statistical analysis	To address health authority requests.	Clinical Study Protocol Synopsis: Study Design Section 6.2 Planned Interim Analysis Section 11.4.9 Timing of Statistical Analysis
• Clarified the justification of sample size for cohort A	Rationale was strengthened to enhance readability based on collaborator feedback.	Section 11.2.1 Cohort A- Justification of Sample Size
• Added a summary of clinical data from the pooled sentinel cohorts from treatment studies (R10933-10987-COV-2066 and R10933 10987-COV-2067) • Clarified that 'healthy subjects' include the elderly or those with stable chronic illness who are considered fit for the study • Clarified the follow-up period for contraception use • Increased frequency of site and/or investigator contact with	To address collaborator comments.	Section 3.2.4 Sentinel Safety Group and Subsequent Safety Reviews Section 3.3 Risk-Benefit Section 5.3 Safety Variables Section 6.1.3 Screening/Baseline Section 6.1.4 Efficacy Assessment Period Section 6.1.5 Follow-up Period Section 6.3.1 Independent Data Monitoring Committee/Data and Safety Monitoring Board Section 6.3.2 Safety Review Committee for REGN 2069/CoVPN3502

subjects who have confirmed SARS-CoV-2 infection • Increased monitoring time after dosing to assess for hypersensitivity and injection site reactions in all subjects who are not in the sentinel group (which has a 4-hour monitoring window) • Clarified that subjects should contact their local emergency department if they experience a true medical emergency • Removed assessment for absenteeism at the screening/baseline visit • Clarified that pregnant subjects are not withdrawn but are followed for safety • Described the specific data to be collected for subjects with a positive RT-PCR result who have medically attended visits (ED, UCC, hospitalization) • Added a household assessment to collect general information about household members • Clarified who can review study records		Section 7.2.1 Inclusion Criteria, #4 Section 7.2.2 Exclusion Criteria, #8, #12, #14 Section 8.9 Prohibited Medications Table 3 Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes #11, #13, #16 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 9.2.1.2 Local Molecular Diagnostic Assay for SARS-CoV-2 Section 9.2.2.3 Assessment of Medically Attended Visits Section 9.2.2.4 Absenteeism Assessment Section 9.2.3.1 Targeted Physical Examination and Vital Signs Section 9.2.3.2 Laboratory Testing
• Clarified the Sponsor access to study results	The Sponsor will not have access to post-baseline patient level study results	Section 8.5 Blinding Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnote #14
• Added ethics committee text relevant sections	The study may include sites in other countries	Section 10.4 Notifying Health Authorities, Institutional Review Board/Ethics Committee and Investigators Section 12.3 Audits and Inspections Section 13.2 Informed Consent Section 13.4 Institutional Review Board/Ethics Committee Section 15.2 Close-out of a Site Section 20 Investigator's Agreement

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARDS	Acute respiratory distress syndrome
BUN	Blood urea nitrogen
CDC	Center for Disease Control
COVID-19	Coronavirus disease 2019
CoVPN	COVID-19 Prevention Network
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
E (protein)	Envelope protein
EAP	Efficacy assessment period
EC	Ethics Committee
ED	Emergency department
EDC	Electronic data capture
ELF	Epithelial lining fluid
EOS	End of study
EUA	Emergency Use Authorization
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized estimation equation
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
IM	Intramuscular
IV	Intravenous
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
M (protein)	Membrane protein
mAb	Monoclonal antibody
MERS-CoV	Middle East respiratory syndrome coronavirus
NAb	Neutralizing anti-drug antibody

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NP	Nasopharyngeal
OP	Oropharyngeal
PK	Pharmacokinetic
PCSV	Potentially clinically significant value
RBC	Red blood cell
RBD	Receptor binding domain
RBQM	Risk-Based Quality Monitoring
Regeneron	Regeneron Pharmaceuticals, Inc.
RT-PCR	Reverse transcription polymerase chain reaction (test)
RT-qPCR	Quantitative reverse transcription polymerase chain reaction (test; refers to the central lab testing in this protocol)
S	Spike protein of the SARS-CoV-2 virus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SDR	Source data review
SDV	Source data verification
SOC	System organ class
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UCC	Urgent care centers
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2
Site Location(s)	Multiple sites in the United States (US) and other countries
Principal Investigator	TBD
Objectives	The primary efficacy objective for cohort A (subjects who are negative for SARS-CoV-2 infection at baseline) is to evaluate the efficacy of REGN10933+REGN10987 (also referred to as casirivimab+imdevimab) compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) that is confirmed by quantitative reverse transcription polymerase chain reaction (RT-qPCR, the central laboratory testing in this study). The primary efficacy objective for cohort B (subjects who are positive for SARS-CoV-2 infection but asymptomatic at baseline) is to evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing COVID-19 symptoms (broad-term). Symptomatic SARS-CoV-2 infections will be defined by strict and broad definitions, as well as by the Center for Disease Control (CDC) case definition. **A strict definition includes**: fever PLUS ≥1 respiratory symptoms (sore throat, cough, shortness of breath), OR 2 respiratory symptoms, OR 1 respiratory symptom PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise). **A broad definition includes:** the signs/symptoms in the strict definition and additional symptoms (23 terms: Feverish, Sore throat, Cough, Shortness of breath/difficulty breathing [nasal flaring*], Chills, Nausea, Vomiting, Diarrhea, Headache, Red or watery eyes, Body aches such as muscle pain or joint pain, Loss of taste/smell, Fatigue [fatigue or general malaise or lethargy*], Loss of appetite or poor eating/feeding, Confusion, Dizziness, Pressure/tightness in chest, Chest pain, Stomach ache (abdominal pain*), Rash, Sneezing, Runny nose, Sputum/phlegm [*Signs and symptoms observed in pediatric subjects]). **The CDC definition is:** at least 2 of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion or runny nose **OR** Any 1 of the following symptoms: cough, shortness of breath, difficulty breathing, new olfactory disorder, new taste disorder **OR** Severe respiratory illness with at least 1 of the following, clinical or radiographic evidence of pneumonia, acute respiratory distress syndrome (ARDS). There are 4 defined cohorts in this study based on the subjects' age and SARS-CoV-2 infection status at baseline, as measured by central lab SARS -CoV-2 RT-qPCR: 1. Cohort A: adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR negative at baseline 2. Cohort A1: pediatric subjects (<12 years) who are SARS-CoV-2 RT--qPCR negative at baseline 3. Cohort B: adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR positive at baseline

4. Cohort B1: pediatric subjects (<12 years) who are SARS-CoV-2 RT--qPCR positive at baseline

Cohort A and Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline

Objectives for cohort A and cohort A1 are for subjects who are seronegative at baseline (by central lab test) unless stated otherwise.

Cohort A Primary Efficacy Objective

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR

Cohort A and Cohort A1 Primary Safety Objective

- To evaluate the safety and tolerability of REGN10933+REGN10987 following subcutaneous (SC) administration compared to placebo

Cohort A and Cohort A1 Secondary Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing a SARS-CoV-2 infection with a high viral load (ie, viral load >4 (log10 copies/mL)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load (ie, viral load >4 (log10 copies/mL)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of treating the index case with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among household contacts in the placebo group (note: This is a cross-study analysis based on only subjects in the placebo group of study R10933-10987-COV-2069 whose index cases participated in study R10933-10987-COV-2067)
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (Centers for Disease Control [CDC] definition) confirmed by RT-qPCR
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (strict-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR viral load

- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To evaluate the impact of treating any SARS-CoV-2 RT-qPCR positive household member with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among their household contacts in placebo group (note: This is a cross-study analysis based on only subjects in placebo group of study R10933-10987-COV-2069 whose index or other household member participated in study R10933-10987-COV-2067 or in cohort B)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected pharmacokinetic (PK) parameters.
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration in seropositive subjects

  To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR (cohort A1)

Cohort B and Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline

Objectives for cohort B and cohort B1 are for subjects who are seronegative at baseline (by central lab test) unless stated otherwise.

Cohort B and Cohort B1 Primary Efficacy Objective

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing COVID-19 symptoms (broad-term)

Cohort B and Cohort B1 Primary Safety Objective

- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration compared to placebo

Cohort B and Cohort B1 Secondary Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing development of:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term; cohort B1)
  - Symptomatic SARS-CoV-2 infection (CDC definition)

- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection:
    - On health care utilization
    - On absenteeism from daily responsibilities (where applicable)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated subjects compared with placebo-treated subjects

Study Design

This is a phase 3 randomized, double-blind, placebo-controlled study in adults, adolescents, and children with household contact exposure to individuals with SARS-CoV-2 infection.

All subjects in the study will be household contacts with close exposure to the first household member known to be infected with SARS-CoV-2 (index case) but who are themselves asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) but may be either positive or negative for SARS-CoV-2 during screening, as assessed by central laboratory RT-qPCR performed at baseline. The index case will have a diagnosis of SARS-CoV-2 infection using a diagnostic test, eg, RT-PCR, antigen test, or other test format (approved or with Emergency Use Authorization [EUA] issued by the US Food and Drug Administration [FDA] or by the equivalent local health authority).

Randomization will be performed by individual study subjects, not by households.

Approximately 3500 adult and adolescent (≥12 years) + 250 pediatric subjects (<12 years) will be enrolled.

Screening/Baseline (day 1)

After subjects provide informed consent, they will be assessed for study eligibility. The screening visit and randomization visit should occur on the same day. If needed, a remote visit may occur to sign the ICF and collect medical history and concomitant medication use, on the day prior to, but within 24 hours of study drug administration, so that the in-person screening and randomization visit may be abbreviated, due to COVID-19 considerations. Study drug administration must occur within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample. On day 1, prior to randomization, a local diagnostic assay for SARS-CoV-2 from appropriate samples will be performed. The results of this assay will be used as a

	stratification factor for randomization to treatment groups (placebo or REGN10933+REGN10987). The requirement for a local diagnostic assay for SARS-CoV-2 is waived when the results are not expected to be available in a timely manner for randomization. Nasopharyngeal (NP) swab sample (swabbing through both nostrils in adults/adolescents and through one nostril in pediatrics <12 years) for central lab testing of SARS-CoV-2 RT-qPCR and blood sample for central lab serology will also be collected and sent to central lab. On day 1, after completing baseline assessments, sample collection, and randomization, all subjects will receive a single dose of study drug. Randomization will be performed on an individual subject basis. In addition to a randomization number, all subjects randomized will be given a household identification number in the case that multiple members of the same household are enrolled and receive study drug. This ensures that correlation among subjects within the same household may be considered in the statistical analysis. Randomization will be performed by site and stratified for assignment of treatment group by test results (positive, negative, or undetermined) of a local diagnostic assay for SARS-CoV-2 (eg, molecular assay such as RT-PCR assay for SARS-CoV-2 or a SARS-CoV-2 antigen test) from appropriate samples, eg, nasopharyngeal (NP), oropharyngeal (OP), nasal, or saliva, and age group (≥12 to <18 years, ≥18 to <50 years, or ≥50 years). For pediatric subjects (<12 years), the weight group (≥20 kg, ≥10 to <20 kg, and <10 kg) will be used as an additional stratification factor. The local diagnostic assay for SARS-CoV-2 must be considered acceptable for clinical use by local standards. If the test has not been approved or received EUA issued by the US FDA or by the equivalent local health authority, then the Sponsor should be consulted. Cohort allocation will be based on central lab baseline SARS-CoV-2 RT-qPCR results for data analysis: cohort A or cohort A1 (negative) and cohort B or cohort B1 (positive). Statistical analyses will be conducted separately in each cohort which will be based on central lab determination of viral positivity and serological status. Subjects will be randomized in a 1:1 allocation ratio to 1 of 2 treatment groups (placebo or REGN10933+REGN10987 [1200 mg (600 mg of each mAb SC)]). This study was preceded by safety review of data from other studies: a safety sentinel group of 30 patients with COVID-19 dosed with REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 8000 mg IV or placebo in the leading phase 1 studies of REGN10933+REGN10987 in the treatment of COVID-19 patients. Randomization in this study did not begin until the Independent Data Monitoring Committee (IDMC) for the treatment studies provided a "study may proceed" conclusion from the IV dosing sentinel group.

Sentinel Group (day 1 to day 4)

Enrollment in this study was carried out in 2 phases:

Sentinel group of approximately 30 adult subjects, irrespective of allocation to cohort A or cohort B.

1. Subjects were monitored for safety on-site for a minimum of 4 hours after administration of the first dose of study drug and then daily via visits to the study site or phone calls for the first 4 days (96 hours). Because REGN10933+REGN10987 had already cleared an adult safety sentinel cohort at higher doses administered IV in previous studies, the sentinel group in this study focused on safety evaluation for injection site reactions and hypersensitivity reactions, and data were reviewed before progressing with enrollment of additional study subjects. The blinded safety data review was led by a designated member of the Regeneron clinical team (generally either the medical monitor or the clinical trial manager) and at a minimum the data review team included the Regeneron Medical Monitor, Study Biostatistician, Global Safety Lead or designee, and the Senior Vice President of Early Clinical Development & Experimental Sciences.
2. Following a conclusion of the blinded safety data review that the study could proceed, the study resumed enrollment.

Pediatric Sentinel Subjects and Staggered Enrollment/Dosing:

Approximately 250 pediatric subjects across all weight-tiered dose ranges will be enrolled. However, since the enrollment of pediatric subjects (<12 years) will end once enrollment of adult and adolescent subjects is complete, the number of pediatric subjects may be adjusted.

Enrollment of pediatric subjects in this study will be carried out in 2 phases each for safety assessment and for confirmation of appropriate level of drug exposure for each weight group.

Pediatric Subjects Safety Sentinel Group

1. Sentinel group will comprise 12 pediatric subjects (by subject number assigned by IWRS; irrespective of allocation to cohort A1 or cohort B1) in 3 weight groups (≥20 kg; 10 kg to <20 kg; <10 kg). Each weight group will have 4 subjects randomized 1:1 to 1 of 2 treatment groups (placebo or REGN10933+REGN10987) and study drug administered first. After all 4 subjects in a weight group complete the sentinel review, enrollment of additional subjects in that weight group will proceed. Pediatric subjects will be monitored for safety on-site for a minimum of 2 hours after administration of study drug and then daily via visits to the study site or phone calls for the first 4 days (96 hours). Because REGN10933+REGN10987 has already cleared an adult safety sentinel cohort at higher doses administered IV in previous studies and the adult safety sentinel in this study, the pediatric sentinel group in this study is focused on safety evaluation for injection site reactions and hypersensitivity reactions. Data will be reviewed before progressing with enrollment of additional pediatric subjects. The blinded safety data review will be led by a designated member of the Regeneron clinical team (generally either the medical monitor or the clinical trial manager) and at a minimum the data review team will include the Regeneron Medical Monitor, Study Biostatistician, Global Safety Lead or designee, and the Senior Vice President of Early Clinical Development & Experimental Sciences.
2. Following a conclusion of the blinded safety data review that the study may proceed for a weight group, the enrollment of pediatric subjects in that weight group will resume. However, close monitoring by the

Safety Review Committee will continue on a periodic cumulative aggregate basis, including stratification to facilitate early and periodic review of data for adolescent subjects (≥12 years to <18 years) and pediatric subjects (<12 years) in each of the weight groups.

Confirmation of Drug Exposure for Pediatric Subjects Weight Groups

1. All pediatric subjects (subset 4 and subset 5) will have samples collected (Schedules A, B, C, and D) in the EAP and Follow-Up periods for drug concentration measurement as well as ADA assessment and clinical laboratory tests (hematology, blood chemistry). The drug concentration data from approximately the first 20 subjects per weight group (<10 kg, 10 to 20 kg, ≥20 kg) will be evaluated to confirm that the REGN10933 and REGN10987 dose for the weight group is providing the expected exposure.
2. Based on simulations using a population PK model using data from adult patients with COVID-19, the proposed doses for the pediatric subjects (see Table below) is expected to match the exposure in adult subjects at SC dose of 1200 mg (600 mg per mAb) in this study. Once the exposure for a dose is confirmed in a weight group, enrollment beyond 25 subjects for this weight group can continue. Based on the results of the drug concentration analyses from up to 20 pediatric subjects receiving active drug in the weight groups, the dose for participating pediatric subjects may be adjusted in 1 or more of the weight-tiered group(s) to ensure drug exposure comparable to adult subjects in this study. If the dose for a particular weight group needs to be adjusted, the new dose for that weight group will used for approximately a subsequent 20 subjects for that weight group. These subjects who received the new dose will have drug concentrations analyzed to confirm that it is providing the expected exposure. When the new dose is started, the subjects will resume dosing according to the next sample collection schedule since the last subject received study drug.

Efficacy Assessment Period (day 1 to day 29)

Efficacy, safety, sample collections, and other study assessments will be performed at specified time points throughout the efficacy assessment period (EAP). If subjects are able to travel and can do so while maintaining social distancing guidelines, subsequent site visits will be conducted; alternatively, telemedicine visits, phone calls, mobile units or home health nurses may be utilized. Throughout the study, biological samples will be obtained by adequately trained and delegated study personnel at study locations where appropriate personal protective equipment (PPE) are available to be used.

Subjects will be instructed to contact the study site staff for any new or changing symptoms or signs possibly related to COVID-19, including fever. The investigator should recommend that subjects (themselves or by their parent/guardian) measure their temperature daily during the EAP, approximately at the same time, and also every time when the subject feels feverish, chills, or sick. Adult subjects may receive automated reminders (eg, text messages to mobile phones; implemented as soon as technologically feasible and when subjects confirm to opt in) in between the weekly visits to prompt them to contact the study site staff as needed.

At each weekly visit, NP swab sample will be collected for SARS-CoV-2 RT-qPCR to be tested at a central lab. The investigator or designee will contact each subject weekly (site visit or telemedicine) to assess the subject's general health, and to document all AEs in general, and any signs and symptoms associated with SARS-CoV-2 infection since the last contact.

Any subject who develops fever, an acute respiratory illness, symptoms related to multisystem inflammatory syndrome in children ([MIS-C] [pediatric subjects <18 years only]), or other symptoms that they feel could be related to COVID-19 should alert the study staff immediately. If the subject experiences a true medical emergency, they should visit their local hospital ED or call the local emergency telephone number (eg, 911 in North America) and contact the clinical site personnel later. Subjects' symptoms must be evaluated by the investigator or designee, which can occur through site visit, mobile unit, home visit, telemedicine, etc. If the investigator or designee suspects SARS-CoV-2 infection, a NP swab sample should be collected and sent for central lab testing. The subject may also be asked to provide a blood sample if it corresponds to a scheduled visit (according to the Schedule of Events).

Subjects with laboratory confirmed SARS-CoV-2 infection during the EAP should be informed as soon as possible and should undergo medical isolation to prevent contact with others to reduce the risk of further transmission. Since these subjects will likely be isolated, the study visits, assessments and sample collections may occur through a variety of methods.

All subjects who have a confirmed SARS-CoV-2 infection will continue to be tested (sample collection weekly) until 2 consecutive confirmed negative SARS-CoV-2 RT-qPCR test results are achieved ≥24 hours apart. This testing may continue through the EAP and into the Follow-up period. For subjects who have a confirmed SARS-CoV-2 infection, the investigator will assess AEs weekly or more frequently than weekly, depending on the clinical status of the subject, as assessed by the investigator or designee (these more frequent AE assessments will be reported as unscheduled visits). The investigator will also collect information for any SARS-CoV-2 infection-related medically attended visits to the ED, UCC, or hospitalization starting from the timepoint of SARS-CoV-2 RT-qPCR positive result.

Subjects presenting with acute illness should be medically managed according to local standard of care as per the discretion of the treating physician.

If a subject is hospitalized for suspected SARS-CoV-2 infection, every effort should be made by the site personnel to collect, as soon as possible, an NP swab sample for central lab SARS-CoV-2 RT-qPCR testing. In subjects where it is not possible to have samples collected for assessment in the central laboratory, study site personnel will attempt to obtain and record information about any positive SARS-CoV-2 assays conducted in local laboratories associated with other medical facilities.

Follow-up Period (day 30 to day 225)

Subjects who remain SARS-CoV-2 RT-qPCR negative throughout the EAP will complete the end of the EAP and enter the Follow-up Period to be followed for 7 months.

Subjects who become SARS-CoV-2 RT-qPCR positive during the EAP will continue to have weekly NP swab samples for SARS-CoV-2 RT-qPCR testing until 2 confirmed negative SARS-CoV-2 RT-qPCR test results are achieved at least 24 hours apart, even after they complete the EAP and enter the study Follow-up Period to be followed for 7 months. In such situations, these visits for sample collection should be characterized as unscheduled visits.

At each scheduled visit, the investigator or designee will contact each subject (site visit or telemedicine) to assess and document the subject's general health, AEs in general and signs and symptoms associated with SARS-CoV-2 infection since the last contact, as described for the EAP.

Study Duration	For each subject, there are 3 study periods: a 1- to 2-day screening/baseline period, a 1-month EAP, and a 7-month follow-up period after the end of the EAP.
End of Study Definition	The end of study is defined as the date the last subject completes the last study visit, withdraws from the study, or is lost to follow-up.
Population	
Sample Size:	**Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline**: Approximately 3150 adult and adolescent subjects will be enrolled. Cohort A is expected to include the majority of study subjects. **Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline:** Approximately 350 adult and adolescent subjects will be enrolled. **Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline:** Approximately 225 pediatric subjects (<12 years) will be enrolled. **Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline**: Approximately 25 pediatric subjects (<12 years) will be enrolled.
Target Population:	Asymptomatic, healthy adults (≥18 years), adolescents (≥12 years to <18 years), and children (<12 years) who are household contacts to the first known household member with a diagnosis of SARS-CoV-2 infection (index case)
Treatments	
Study Drug	REGN10987 and REGN10933
Dose/Route/Schedule:	**Adult and adolescent subjects (≥12 years):** • 1200 mg (600 mg of each mAb) / SC / single dose on day 1

Weight-Tiered Dose Groups for Pediatric Subjects <12 Years of Age

Weight-Tiered Dose Group	Total Dose (mg)	Route of Administration	Total Number of Injections	Total Volume (mL) of Injection
≥40 kg	1200 (600 per mAb)	SC[1]	4	10 (5 per mAb)
≥20 to <40 kg	792 (396 per mAb)	SC[1]	4	6.6 (3.3 per mAb)
≥10 to <20 kg	408 (204 per mAb)	SC[1]	2 or 4	3.4[2] (1.7 per mAb)
≥5 to <10 kg[3]	144 (72 per mAb)	IM	1 or 2	1.2[4] (0.6 per mAb)
≥2.5 to <5 kg[3]	96 (48 per mAb)	IM	1	0.8 (0.4 per mAb)
<2.5 kg[3]	48 (24 per mAb)	IM	1	0.4 (0.2 per mAb)

1. Investigators have the option to use an infusion pump for SC administration of study drug containing the combined volume with both mAbs.
2. If the Investigator prefers not to exceed 1 mL per syringe, then study drug may be administered using 2 syringes for each mAb (ie, 4 injections), one with 0.8 mL and another with 0.9 mL for each mAb. If the Investigator prefers to use only 2 syringes (ie, 2 injections), the 1.7 mL administered in each syringe will contain a different mAb.
3. Investigators have the option to administer the dose in a single syringe containing the combined volume with both mAbs.
4. If the Investigator prefers not to exceed 1 mL per syringe, then study drug may be administered using 1 syringe for each mAb. If the Investigator prefers to use 1 syringe, the1.2 mL administered in 1 syringe should be combined volume of 0.6 mL of each mAb.

Placebo	Matching solution
Route/Schedule:	SC / single dose on day 1 IM / single dose on day 1 for pediatric subjects <10 kg

Endpoint	Endpoints are specified for study cohorts. Symptomatic SARS-CoV-2 infection is determined by a positive central lab SARS-CoV-2 RT-qPCR result during the EAP with signs/symptoms occurring within ±14 days of a positive RT-qPCR. The "strict-term", "broad-term", and CDC definitions for signs/symptoms of SARS-CoV-2 infection are presented earlier in Objectives.
Primary Endpoints:	**Cohort A and Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline** The endpoints are for subjects who are seronegative at baseline (based on central lab test) unless stated otherwise. ***Cohort A Primary Efficacy Endpoint*** • Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP ***Cohort A and Cohort A1 Primary Safety Endpoint*** • Proportion of subjects with treatment-emergent adverse events (TEAEs) and severity of TEAEs
Secondary Endpoints:	**Cohort A and Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline** ***Cohort A Key Secondary Endpoints*** • Proportion of subjects with viral load >4 ($\log_{10}$ copies/mL) in nasopharyngeal (NP) swab samples during the EAP • Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP • Number of weeks of high-viral load >4 ($\log_{10}$ copies/mL) in NP swab samples during the EAP • Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP • Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP • Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 versus placebo in study R1033-10987-COV-2067) ***Cohort A and Cohort A1 Other Secondary Endpoints*** • Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (CDC definition) during the EAP • Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (CDC definition) during EAP • Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (strict-term) during the EAP • Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (strict-term) during the EAP

- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection at each week in the EAP
- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad term) at each week in the EAP
- Time-weighted average of viral load (log_{10} copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab sample (that has an onset during the EAP) until the third weekly visit after the first positive test during the EAP

  Note: Only for RT-qPCR positive subjects during the EAP in the seronegative modified full analysis set for cohort A (seronegative mFAS-A)
- Time-weighted average of viral load (log_{10} copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab sample (that has an onset during the EAP) until the second weekly visit after the first positive test during the EAP

  Note: Only for RT-qPCR positive subjects during the EAP in the seronegative mFAS-A
- Maximum SARS-CoV-2 RT-qPCR viral load (log_{10} copies/mL) in NP swab samples among individuals with ≥1 RT-qPCR positive that has an onset during the EAP
- SARS-CoV-2 RT-qPCR viral load (log_{10} copies/mL) in NP swab samples corresponding to the onset of first positive RT-qPCR during the EAP
- Area under the curve (AUC) in viral load (log_{10} copies/mL) from the first positive SARS-CoV-2 RT-qPCR NP swab sample detected during the EAP until the first confirmed negative test (testing that occurs after the EAP will be included if necessary to achieve a negative test result)

  Note: Only for RT-qPCR positive subjects during the EAP in the seronegative mFAS-A
- Number of medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Proportion of subjects with at least 1 COVID-19-related hospitalization or emergency room visit associated a positive RT-qPCR during the EAP, or all-caused death
- Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Number of days of hospital and intensive care unit (ICU) stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (students), daycare or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP

- Proportion of subjects in the placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with at least 1 household member participating either in study R10933-10987-COV-2067 or in cohort B (comparison of those whose households members receive REGN10933+REGN10987 versus placebo in study R1033-10987-COV-2067 or in cohort B)

Additional Cohort A1 Secondary Efficacy Endpoint

- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
- Proportion of subjects with viral load >4 ($\log_{10}$ copies/mL) in nasopharyngeal (NP) swab samples during the EAP
- Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
- Number of weeks of high-viral load >4 ($\log_{10}$ copies/mL) in NP swab samples during the EAP
- Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
- Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 versus placebo in study R1033-10987-COV-2067)

Cohort A and Cohort A1 Secondary Safety Endpoints

- Proportion of baseline seropositive subjects (based on central lab test) with TEAEs and severity of TEAEs
- Incidence and severity of symptomatic SARS-CoV-2 infection in seronegative and seropositive subjects (based on central lab test) in both the EAP and follow-up periods

Cohort A and Cohort A1 Pharmacokinetic and Immunogenicity Endpoints

- Concentrations of REGN10933and REGN10987 in serum over time and selected PK parameters in both seronegative and seropositive subjects (based on baseline central lab test)
- Immunogenicity as measured by anti-drug antibodies (ADA) and neutralizing antibodies (NAbs) to REGN10933 and REGN10987 over time in both seronegative and seropositive subjects (based on baseline central lab test)

Cohort B and Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline

The endpoints are for all subjects who are seronegative at baseline (based on central lab test), unless stated otherwise.

Cohort B Primary Efficacy Endpoint

- Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

Cohort B Key Secondary Efficacy Endpoints

- Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of high viral load >4 ($\log_{10}$ copies/mL) in NP swab samples during the EAP

Cohort B and Cohort B1 Other Secondary Efficacy Endpoints

- Proportion of subjects who subsequently develop signs and symptoms (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Proportion of subjects who subsequently develop signs and symptoms (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of symptomatic SARS-CoV-2 infection (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of symptomatic SARS-CoV-2 infection (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Proportion of subjects with viral load >4 ($\log_{10}$ copies/mL) in NP swab samples during the EAP
- Change in viral load ($\log_{10}$ copies/mL) from baseline to day 8 visit in NP swab samples
- Change in viral load ($\log_{10}$ copies/mL) from baseline to day 15 visit in NP swab samples
- Time-weighted average change from baseline in viral load ($\log_{10}$ copies/mL) in NP swab samples until the day 22 visit.
- Area under the curve (AUC) in viral load ($\log_{10}$ copies/mL) in NP swab samples from baseline to the first confirmed negative test
- Maximum SARS-CoV-2 RT-qPCR viral load ($\log_{10}$ copies/mL) in NP swab samples during the EAP
- Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP

- Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Proportion of subjects with at least 1 COVID-19 related hospitalization or emergency room visit associated with a positive RT-qPCR at baseline or during the EAP, or all-cause death

Additional Cohort B1 Secondary Efficacy Endpoints

- Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks with high viral load >4 (log_{10} copies/mL) in NP swab samples at during the EAP

Cohort B and Cohort B1 Secondary Safety Endpoints

- Proportion of subjects with TEAEs and severity of TEAEs
- Incidence and severity of symptomatic SARS-CoV-2 infection in both the EAP and follow-up periods

Cohort B and Cohort B1 Pharmacokinetic and Immunogenicity Endpoints

- Concentrations of REGN10933 and REGN10987 in serum over time and selected PK parameters in both seronegative and seropositive subjects (based on baseline central lab test)
- Immunogenicity as measured by ADAs and NAbs to REGN10933 and REGN10987 over time in both seronegative and seropositive subjects (based on baseline central lab test)

Procedures and Assessments	**Screening/Baseline Procedures:** The following procedures will be performed for the purpose of determining study eligibility or characterizing the baseline population: demographics (eg, age, sex, race, weight, height, etc), medical history, local diagnostic assay for SARS-CoV-2, query for risk for SARS-CoV-2 infection, and household assessment in which subjects will be asked to provide general information about the household members. The investigator or sub-investigator will verify that the subject tests negative or positive by a local diagnostic assay for SARS-CoV-2 (eg, molecular assay such as RT-PCR assay for SARS-CoV-2 or a SARS-CoV-2 antigen test using an appropriate sample such as NP, nasal, OP, or saliva). The local diagnostic assay for SARS-CoV-2 must be considered acceptable for clinical use by local standards. If the test has not been approved or received EUA issued by the US FDA or by the equivalent local health authority, then the Sponsor should be consulted. The use of a RT-PCR assay is highly recommended. The local diagnostic test result, specimen type (eg, nasal swab), assay type, and date of test will be recorded in the eCRF. The sample type collected is dependent on local lab requirements. **Efficacy Procedures:** Nasopharyngeal Swab SARS-CoV-2 RT-qPCR Test (Central Lab): Nasopharyngeal swab sample will be collected from subjects to determine presence or absence of SARS-CoV-2 virus and to determine the relative quantification in viral load. COVID-19 Symptomology (Broad Term, Strict Term, CDC definition): During each scheduled or unscheduled visit/contact, the investigator or sub-investigator, or designee (ie, nurse practitioner in countries where allowed by local law) will query the subject and/or subject's parent or guardian about adverse events the subject is experiencing or has experienced since the last visit/contact (eg, within the prior week if it is a weekly scheduled visit) and ask about all of the signs and symptoms associated with these adverse events including the start date, end date and severity of each. The investigator should avoid querying the subject and/or subject's parent or guardian by running a check-list of signs and symptoms, but rather allow the subject and/or subject's parent or guardian to spontaneously report everything that they presented. All signs and symptoms related to the AEs, along with the corresponding start date, end date and severity should be documented in the subject's medical records (source document). As signs and symptoms may appear and resolve on different days and may precede or occur after the collection of NP swab sample for the SARS-CoV-2 RT-qPCR test, it is important that this detailed information be captured in the source document. Independent of the results (positive or negative) of the SARS-CoV-2 RT-qPCR tests performed on samples collected from study subjects during the weekly or unscheduled visits, all adverse events must be documented in the AE CRF. Signs and symptoms related to the adverse events reported in the AE CRF and confirmed to be temporally related to a positive SARS-CoV-2 RT-qPCR test collected from the subject's NP swab sample will be reported on a separate CRF (individual sign or symptom with start date and end date, and associated severity).

Strict-term COVID-19 signs and symptoms, defined as:

- fever (≥38°C) PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath);

  OR

- 2 respiratory symptoms (sore throat, cough, shortness of breath);

  OR

- 1 respiratory symptom (sore throat, cough, shortness of breath) PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise).

- Broad-term COVID-19 signs and symptoms: defined as any of the 23 symptoms (listed earlier in the Objectives) or fever (≥38°C).
- The CDC definition: defined as at least 2 of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion or runny nose OR Any 1 of the following symptoms: cough, shortness of breath, difficulty breathing, new olfactory disorder, new taste disorder OR Severe respiratory illness with at least 1 of the following, clinical or radiographic evidence of pneumonia, ARDS.

<u>Medically Attended Visits</u>: Subjects and/or their parent/guardian (as appropriate) who become SARS-CoV-2 RT-qPCR positive will be queried on any SARS-CoV-2 infection-related medically attended visits to the ED, UCC, or hospitalization. The assessment of medically attended visits to ED, UCC or hospitalization will be performed from the time the subject first becomes SARS-CoV-2 RT-qPCR positive or from the time they develop symptoms suspected to be COVID-19 (later confirmed by RT-qPCR positive results) until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or of until the end of study visit.

<u>Absenteeism Assessment:</u> Subjects and/or their parent/guardian who are or become SARS-CoV-2 RT-PCR positive during the EAP will be queried on any SARS-CoV-2 infection-related absenteeism. Data include absenteeism (where applicable) defined as number of days missed for daily responsibilities, including work (employed adults) or school (students), daycare, or family obligations/responsibilities (childcare or eldercare) due to COVID-19.

Safety Procedures:

<u>Targeted Physical Examination and Vital Signs</u>: The targeted physical examination and vital signs include measurements of body temperature, blood pressure (measured after the subject has been resting quietly for at least 5 minutes and may be obtained from a seated or supine position), pulse rate, and respiratory rate, and examination of the oropharynx, skin, heart, lungs and any other system(s) depending on any complaints or concerns expressed by the subjects.

<u>Laboratory Testing</u>: samples for blood chemistry, hematology, and urinalysis (only for adolescent/adult subjects) will be collected and analyzed. For all women of childbearing potential, a urine pregnancy test will be performed onsite and any positive urine pregnancy test will be confirmed with a serum pregnancy test at the central laboratory.

	Other Procedures: Drug Concentration and Immunogenicity measurements: Dense sample and sparse sample collection for drug concentration measurement will be performed in subsets of subjects. Samples for ADA and NAb assessment will be collected at various times throughout the study. Any unused serum samples may be used for exploratory research. Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies: In order to assess the impact of baseline humoral immunity/antibody response to SARS-CoV-2 on REGN10933+REGN10987 efficacy to prevent SARS-CoV-2 infection, serum anti-SARS-CoV-2 will be measured at baseline, including but not limited to those which detect antibodies against the S protein and/or the N protein and/or neutralization assays. Samples will be collected from adult and pediatric subjects (<18 years). Exploratory Pharmacodynamic/Biomarker and Serum/Plasma Samples for Research: Samples for assessment of pharmacodynamic and exploratory research will be collected from adult and adolescent subjects. Pharmacogenomic Analysis (Optional): Adult and pediatric subjects (<18 years and >10 kg) subjects may participate in an optional genomics sub-study (separate informed consent required). Blood sample for RNA and DNA will be collected for this substudy.
Statistical Plan	**Justification of Sample Size** An administrative assessment for assumption verification and sample size estimation for cohort A will be conducted using unblinded descriptive analyses without performing any formal statistical hypothesis testing. Analyses will be conducted in the group of cohort A subjects randomized from study initiation through the date of randomization that are associated with 30 RT-PCR events amongst cohort A seronegative subjects during the EAP (approximately 600 subjects overall regardless of baseline serology status[eg, seronegative, seropositive, or other (eg, borderline or undetermined, etc)]). The subjects evaluated in this descriptive analysis will not be included for the final efficacy analyses, however, these subjects will be included in the safety analyses. To maintain operational efficiencies and because of the progressive rollout of SARS-CoV-2 vaccination which may change the dynamics of virus transmission/infection in the near future, enrollment into the study will not be paused while the administrative assessment is performed and it is estimated that the total enrollment may reach approximately 3500 subjects. The following justification of sample size in cohort A with the assumption of reduction of symptomatic infection is based on the results from the administrative assessment described below. For the purpose of the study analysis, cohort A and cohort B are independent with separate type I error control for each cohort. ***Cohort A: Adult and Adolescent Subjects (≥12years) Who Are SARS-CoV-2 RT-qPCR Negative*** In cohort A, subjects are randomized in a 1:1 allocation ratio to REGN10933+REGN10987 or placebo. The primary hypothesis is the reduction in the proportion of symptomatic RT-qPCR (broad-term) confirmed SARS-CoV-2 infections in seronegative subjects. To calculate the sample size required to achieve at least 90% power for seronegative subjects in cohort A, it is assumed that the statistical hypothesis will be tested in a 2-sided test. Based on the administrative assessment results among 409 seronegative subjects in cohort A, a 50% reduction of infections (symptomatic or asymptomatic) compared to the placebo group and a 100% reduction of symptomatic infections compared to placebo group were observed. Due to the small sample size in the

administrative assessment, it was assumed, for the purpose of assessing study power, that an approximately 50% reduction or greater in symptomatic infections compared to the placebo group will be expected for the final primary efficacy analysis.

In this household study design, the number of subjects per household, the correlation between subjects and symptomatic infection rates within a household are unknown. To detect a relative risk of 0.5 (ie, 50% reduction of the assumed 10% attack rate in the placebo arm), equivalent to an odds ratio of 0.47, power was also calculated compared to the boundary p-value of 0.05 based on 2000 simulations in 1248 subjects from 430 households (ie, assuming an average household size of 2.9 seronegative subjects by varying degrees of correlation within household. In all cases, the power of the study is >90% using a generalized linear model with the generalized estimation equation (GEE) approach and assuming a compound symmetry covariance matrix.

At least 1980 subjects will need to be enrolled in cohort A to have a minimum of 1248 seronegative subjects, assuming that 10% of subjects drop out, 30% of subjects are seropositive at baseline.

Cohort A1: Pediatric Subjects (<12 years) with SARS-CoV-2 RT-qPCR Negative

Approximately up to a total of 250 pediatric subjects (<12 years) will be enrolled in this study. Of the 250 subjects, 90% (225/250) are expected to be enrolled in this cohort (ie, central lab RT-qPCR negative at baseline) for evaluating the drug concentration and exposure, and safety. The actual number of subjects in this cohort will depend on the actual percentage of subjects with a baseline negative RT-qPCR enrolled. No statistical hypothesis tests will be performed.

Cohort B: SARS-CoV-2 RT-qPCR Positive

The primary endpoint in asymptomatic, seronegative subjects in cohort B is the proportion of subjects who subsequently develop signs and symptoms (broad term) within 14 days of a positive RT-qPCR test result at baseline or during the EAP.

The sample size of cohort B is based on the frequency of finding positive subjects while enrolling cohort A and assumes that approximately 10% of subjects in a household are already positive for SARS-CoV-2 by RT-qPCR at baseline. Among approximately 3500 adult and adolescent subjects that are anticipated to be enrolled in cohort A or cohort B, the number of subjects expected in cohort B is approximately 220 or greater, including 200 seronegative subjects. Assuming that 50% of infected placebo subjects at baseline will develop symptoms, 200 seronegative subjects in cohort B will provide >90% power to detect a relative risk of 0.5, using a 2-sided Fisher's exact test at an alpha level of 0.05.

Cohort B1: Pediatric Subjects (<12 years) with SARS-CoV-2 RT-qPCR Positive

Approximately up to a total of 250 pediatric subjects (<12 years) will be enrolled in this study. Of 250 subjects, 10% (25/250) are expected to be enrolled in this cohort (ie, central lab RT-qPCR positive at baseline) for evaluating the drug concentration and exposure, and safety. The actual number of subjects in this cohort will depend on the actual percentage of subjects with a baseline positive RT-qPCR enrolled. No statistical hypothesis tests will be performed.

Efficacy Analysis Sets

Seronegative Modified Full Analysis Set (Seronegative mFAS-A) – Cohort A

The seronegative modified full analysis set for cohort A (seronegative mFAS-A) includes all randomized subjects aged 12 years and older who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects included in the administrative assessment analysis are excluded from the seronegative mFAS-A population.

Subjects will be analyzed based on the randomized treatment assignment. The seronegative mFAS-A population is the primary analysis population for the primary and secondary endpoints for cohort A of this study unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-A1) – Cohort A1

The seronegative modified full analysis set for cohort A1 (seronegative mFAS-A1) includes all randomized subjects aged less than 12 years who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects will be analyzed based on the randomized treatment assignment. The efficacy endpoints for cohort A1 will be analyzed using the seronegative mFAS-A1 unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B) – Cohort B

The seronegative modified full analysis set for cohort B (seronegative mFAS-B) includes all randomized subjects aged 12 years and older who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) and are asymptomatic at baseline. Subjects will be analyzed based on the randomized treatment assignment. The primary and secondary efficacy endpoints for cohort B will be analyzed using the seronegative mFAS-B unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B1) – Cohort B1

The seronegative modified full analysis set for cohort B1 (seronegative mFAS-B1) includes all randomized subjects aged less than 12 years who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) at baseline. Subjects will be analyzed based on the randomized treatment assignment. The efficacy endpoints for cohort B1 will be analyzed using the seronegative mFAS-B1 unless specified otherwise.

Primary Efficacy Analysis (Cohort A)

The primary efficacy endpoint will be analyzed in the seronegative mFAS-A population. In order to account for the correlation among subjects within a household and control the associated type 1 error inflation, a generalized linear model will be used to estimate the odds ratio between the treatment groups by using the GEE approach. This model estimates a single within-household correlation coefficient. The model will include the fixed category effects of treatment group (placebo versus REGN10933+REGN10987), region (US vs ex-US), and age (≥12 to <50, ≥50 years). The model will use a compound symmetry covariance matrix and estimate the odds ratio between the treatment groups and corresponding 95% CI and p-value. If the GEE model fails to converge due to most households containing only a single study subject in seronegative mFAS-A or the percentage of households with only a single study subject is 70% or more, then a logistic regression model will be used, with treatment, region, and age group as fixed effects.

Subjects with COVID-19 symptoms that are missing a central lab determined RT-qPCR test during the EAP (eg. are too sick to go to the study site) but have a positive SARS-COV-2 test from a local lab (eg. in the hospital) will be considered as having a symptomatic infection if any of the symptoms occurred within 14 days of the positive SARS-COV-2 test.

Additional sensitivity analyses for missing data are described in the protocol.

Control of Multiplicity

The overall type I error will be controlled in each of the seronegative mFAS-A and seronegative mFAS-B independently at a 2-sided 5% significance level.

Seronegative mFAS-A Subjects

The overall type I error will be controlled for the primary hypothesis in cohort A based on a 2-sided test at an alpha level of 0.05 as follows:

H0: There is no treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP.

H1: There is a treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP

If the primary efficacy endpoint in cohort A is statistically significant, the alpha level of 0.05 will be released for the key secondary endpoints in cohort A. The hierarchy testing sequence of key secondary endpoints is presented in the protocol and statistical analysis plan (SAP).

Cohort B: SARS-CoV-2 RT-qPCR Positive

The overall type I error will be controlled for the primary hypothesis in cohort B based on a 2-sided test at an alpha level of 0.05 as follows:

H0: There is no treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP.

H1: There is a treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP.

If statistical significance is established for the primary efficacy endpoint in cohort B, a hierarchical testing procedure will be applied to the key secondary endpoints in cohort B at a 2-sided 0.05 significance level. The order of testing sequence for key secondary endpoints is presented in the protocol and SAP.

Safety Analysis

Safety and tolerability will be summarized for each cohort and will also be summarized by baseline serology status for all adults, adolescent subjects, and pediatric subjects.

1. INTRODUCTION

1.1. Emergence of SARS-CoV-2 and COVID-19

Coronaviruses are a family of enveloped, single-stranded RNA viruses. In recent decades, two highly pathogenic strains of coronavirus were identified in humans: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). These viruses were found to cause severe, and sometimes fatal, respiratory illness (Cui, 2019) (Fehr, 2015).

In December 2019, a pneumonia of unknown cause was identified in clusters of patients in Wuhan City, China. A novel enveloped RNA betacoronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in these patients, and the viral infection was later designated coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO, 2020b) (Zou, 2020). As of June 2020, more than 7.6 million confirmed cases of COVID-19 have been reported globally (WHO, 2020a). This rapidly-spreading, worldwide outbreak prompted the WHO to declare COVID-19 a pandemic and public health emergency of international concern on 11 March 2020.

1.2. Populations at Increased Risk of SARS-CoV-2 Infection Among Household Contacts of a Person Infected with SARS-CoV-2

Efforts to control the pandemic have resulted in widespread shelter-in-place orders. Transmission of SARS-CoV-2 occurs primarily through person-to-person contact and respiratory droplet transmission (Lai, 2020). Household contacts of a person infected with SARS-CoV-2 are at a high risk for acquiring infection, with transmission rates ranging from approximately 10% to 15%. One US study reported a household attack rate of 29%, 42% among children (<18 years) of the SARS-CoV-2-infected patient, suggesting that children and adolescents are especially vulnerable to household transmission of SARS-CoV-2 (Lewis, 2020). Pregnant women, in particular, are at increased risk for developing severe COVID-19 and have been shown to have a higher rate of hospitalization, need for mechanical ventilation, and ICU admission than non-pregnant women (Ellington, 2020) (Knight, 2020)(Woodworth, 2020). Neonatal transmission of SARS-CoV-2 has also been reported (Vivanti, 2020). Therefore, pregnant women should be considered for inclusion in COVID-19 prophylaxis efforts. Although it has been reported that the majority of individuals who acquire infection from household contacts develop symptoms of COVID-19 (Burke, 2020) (Jing, 2020), (Bi, 2020) (Li, 2020b), in a cruise ship setting, the majority of persons who are asymptomatic at the time of testing remain asymptomatic throughout the course of the infection (ie, until reverse transcription polymerase chain reaction (RT-PCR) results are negative (Sakurai, 2020). Prophylaxis is urgently needed to reduce transmission rates and/or reduce the occurrence of symptomatic disease. Ideally, prophylaxis would need to be given as soon as possible after a known exposure, as the duration of time between symptomatic infection in the source individual and the development of symptoms in newly infected individual is thought to be approximately 5 days, with a possible range of 2 to14 days (Lauer, 2020) (Li, 2020a). Animal models suggest that SARS-CoV-2 RT-PCR in nasopharyngeal (NP) samples become positive within a few days after infection (Rockx, 2020). An ideal agent for prophylaxis should be fast acting and highly effective and should protect against multiple viral variants. A monoclonal antibody (mAb) combination therapy, with two different monoclonal antibodies that bind distinct regions of the portion of the

SARS-CoV-2 spike (S) protein that bind to and facilitate entry into host cells, has been developed in order to achieve these goals. A mAb combination against SARS-CoV-2 for post-exposure prophylaxis that can either prevent the development of disease or reduce viral acquisition or viral load could be key to reducing transmission of the virus and limiting symptoms and adverse outcomes following infection.

1.3. The Role of Spike Protein in SARS-CoV-2 Pathogenesis

Coronaviruses consist of an RNA genome packaged in nucleocapsid (N) protein surrounded by an outer envelope. The envelope is comprised of membrane (M) protein and envelope (E) protein, which are involved in virus assembly, and spike (S) protein, which mediates entry into host cells. S proteins form large trimeric projections, providing the hallmark crown-like appearance of coronaviruses. S protein trimers bind to a host receptor and, after priming by cellular proteases, mediate host–virus membrane fusion (Li, 2016). The S protein appears to be central to viral infectivity by SARS-CoV-2. SARS-CoV-2 S protein binds the host protein angiotensin-converting enzyme 2 (ACE2) with high affinity, and in cell assays and animal models can utilize ACE2 as a functional receptor for host cell entry (Ou, 2020) (Hoffmann, 2020) (Walls, 2020).

Blockade of host cell entry through the use of neutralizing antibodies against S protein is a viable mechanistic strategy shown to reduce viral infectivity of SARS-CoV and MERS-CoV (Jiang, 2020). In light of the likely pivotal role of spike protein in the pathogenesis of SARS-CoV-2, a number of efforts are underway to develop antibodies and vaccines that target the S protein of this novel coronavirus.

1.4. REGN10933+REGN10987: Fully Human Monoclonal Antibodies that Target SARS-CoV-2 S Protein

Regeneron Pharmaceuticals, Inc (Regeneron) is currently developing fully human, neutralizing mAbs directed against the S protein of SARS-CoV-2, for the treatment and prevention of SARS-CoV-2 infection. REGN10933 and REGN10987 are fully human, IgG1 mAbs that bind to distinct regions of the receptor binding domain (RBD) of the SARS-CoV-2 S protein and block interaction with ACE2. REGN10933 and REGN10987 (also referred to as casirivimab+imdevimab) exhibit potent neutralization and can bind simultaneously to the S protein RBD. When co-administered as combination therapy, REGN10933+REGN10987 prophylaxis is anticipated to neutralize SARS-CoV-2 with a reduced likelihood of viral escape due to genetic mutations. In vitro experiments designed to specifically test for viral escape under selective pressure have shown that the combination of REGN10933+REGN10987 was resistant to escape while some single anti-Spike protein monoclonal antibodies were vulnerable to escape. REGN10933+REGN10987 combination therapy thus represents a promising prophylaxis strategy to reduce SARS-CoV-2 infection upon exposure to SARS-CoV-2.

1.5. A Randomized, Placebo-Controlled Study of Anti-Spike Protein Monoclonal Antibodies as Post-Exposure Prophylaxis and Pre-emptive Therapy in Household Contacts

Many therapeutic agents have been studied in the context of other coronaviruses (SARS-CoV and MERS-CoV), including corticosteroids, type 1 interferons, convalescent plasma, ribavirin, lopinavir/ritonavir, proteases, and agents targeting viral entry proteins, with generally inconsistent findings of efficacy (Sanders, 2020). Several of these therapies, as well as a number of other potential treatments and vaccines, are currently under investigation for the treatment of SARS-CoV-2. There is currently only 1 approved treatment for COVID-19, remdesivir, approved for use in patients 12 years of age and older requiring hospitalization or other comparable acute care setting. Additionally, there are currently only 3 therapies for which the FDA has issued an Emergency Use Authorization (EUA): convalescent plasma for use in hospitalized patients, bamlanivimab (a monoclonal antibody against SARS-COV-2) for use in outpatients 12 years of age and older and who are at high risk for progressing to severe COVID-19 and/or hospitalization, and REGN10933+REGN10987 for use in outpatients 12 years of age and older with confirmed mild to moderate COVID-19 who are also at high risk for progressing to severe COVID-19 and/or hospitalization. Currently, however, there is no approved prophylaxis for COVID-19 nor for patients that are infected with SARS-CoV-2 but are asymptomatic. Given the speed at which this outbreak has spread and how it has impacted almost every community globally, there is an urgent need to develop safe and efficacious interventions to slow the spread of the SARS-CoV-2 virus and decrease adverse outcomes associated with symptomatic disease.

This is a pivotal phase 3 randomized, double-blind, placebo-controlled study in adult subjects and pediatric subjects (<18 years of age) with household contact exposure to individuals with SARS-CoV-2 infection in geographic areas with an active COVID-19 outbreak. This study is designed to assess the efficacy and safety of co-administered REGN10933+REGN10987 combination therapy ("REGN10933+REGN10987") to reduce the proportion of SARS-CoV-2 infections and prevent the development of COVID-19 disease (symptomatic SARS-CoV-2 infection), after household exposure to individuals with SARS-CoV-2 infection. Safety, tolerability, pharmacokinetics (PK), and immunogenicity of REGN10933+REGN10987 will also be evaluated.

For more information regarding the rationale for the study design and dose selection, refer to Section 3.2. Additional background information on the study drugs and the overall development program can be found in the Investigator's Brochure (IB).

2. STUDY OBJECTIVES

All subjects in the study will be household contacts of the first known household member to be infected with SARS-CoV-2 infection (index case) but who are themselves asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening.

For analysis of endpoints, there are 4 defined cohorts based on the subjects' SARS-CoV-2 infection status at baseline, as measured by central lab SARS-CoV-2 RT-qPCR (quantitative reverse transcription polymerase chain reaction) and on the subject's age:

1. Cohort A: adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR negative at baseline
2. Cohort A1: pediatric subjects (<12 years) who are SARS-CoV-2 RT-qPCR negative at baseline
3. Cohort B: adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR positive at baseline
4. Cohort B1: pediatric subjects (<12 years) who are SARS-CoV-2 RT-qPCR positive at baseline

Results of the local diagnostic assay for SARS-CoV-2 from appropriate samples (eg NP, oropharyngeal [OP], or nasal or saliva) at baseline will be used as stratification factors for randomization and treatment group allocation, but not for the designation of cohorts for data analysis.

Cohorts are described in Section 3.2.3 and are defined in Section 6.1.6. Study objectives and endpoints are specified based on their SARS-CoV-2 RT-qPCR results at baseline: cohort A and cohort A1 (negative results) or cohort B and cohort B1 (positive results).

The "strict-term", "broad-term", and CDC definitions for signs/symptoms of SARS-CoV-2 infection are presented in Section 9.2.2.2.

2.1. Cohort A and Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline

Objectives are for subjects who are seronegative at baseline (based on central lab test) unless stated otherwise.

2.1.1. Primary Objectives

2.1.1.1. Cohort A Primary Efficacy Objective

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR

2.1.2. Cohort A and Cohort A1 Primary Safety Objective

- To evaluate the safety and tolerability of REGN10933+REGN10987 following subcutaneous (SC) administration compared to placebo

2.1.3. Cohort A and Cohort A1 Secondary Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing a SARS-CoV-2 infection with a high viral load (ie, viral load >4 (log10 copies/mL)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load (ie, viral load >4 (log10 copies/mL)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of treating the index case with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among household contacts in the placebo group (This is a cross-study analysis based on only subjects in placebo group of study R10933-10987-COV-2069 whose index cases participated in study R10933-10987-COV-2067)
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (Center for Disease Control [CDC] definition) confirmed by RT-qPCR
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (strict-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To evaluate the impact of treating any SARS-CoV-2 RT-qPCR positive household member with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among their household contacts in placebo group (note: This is a cross-study analysis based on only subjects in placebo group of study R10933-10987-COV-2069 whose index or other household member participated in study R10933-10987-COV-2067 or in cohort B)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters

- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration in seropositive subjects
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR (cohort A1)

2.1.4. Cohort A and Cohort A1 Exploratory Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing SARS-CoV-2 infection assessed by seroconversion in baseline seronegative subjects
- To explore the impact of REGN10987+REGN10933 compared to placebo:
  - On humoral immune response to SARS-CoV-2 infection
  - On measures of infectivity of SARS-CoV-2 as assessed in experimental laboratory assays
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 infection in subjects who are seropositive at baseline:
  - Prevention of symptomatic infection (strict-term)
  - Prevention of symptomatic infection (broad-term)
  - Prevention of symptomatic infection (CDC definition)
  - Prevention of symptomatic infection (strict-term, CDC definition, or broad-term) or asymptomatic infection
- To explore the relationships between REGN10933+REGN10987 exposure and selected clinical efficacy and safety endpoints and/or biomarkers in seropositive and seronegative subjects
- To assess viral genetic variation in SARS-CoV-2 in subjects with a positive SARS-CoV-2 RT-qPCR
- To explore biomarkers (including host genome variants) associated with safety and efficacy of REGN10933+REGN10987 and to study SARS-CoV-2 (cohort A only)
- To evaluate the impact of treating any household member with anti-SARS-CoV-2 monoclonal antibody on the incidence of SARS-CoV-2 infection among their household contacts. The monoclonal antibody treatment considered for this analysis are any EUA approved antibody any EUA approved antibody including REGN10933+REGN10987 (within or outside of the study R10933-R10987-COV-2067).

2.2. Cohort B and Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline

Objectives for cohort B and cohort B1 are for subjects who are seronegative at baseline (by central lab test) unless stated otherwise.

2.2.1. Cohort B Primary Efficacy Objective

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing COVID-19 symptoms (broad-term)

2.2.2. Cohort B and Cohort B1 Primary Safety Objective

- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration compared to placebo

2.2.3. Cohort B and Cohort B1 Secondary Objectives

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing development of:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term; cohort B1)
  - Symptomatic SARS-CoV-2 infection (CDC definition)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated subjects compared with placebo-treated subjects

2.2.4. Cohort B and Cohort B1 Exploratory Objectives

- To evaluate the impact of REGN10933+REGN10987 compared to placebo in seropositive subjects in preventing:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term)
  - Symptomatic SARS-CoV-2 infection (CDC definition)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in seropositive subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in seropositive subjects on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To explore the impact of REGN10987+REGN10933 compared to placebo in subjects, by their baseline serology test status (eg, seropositive or seronegative, based on central lab test) on SARS-CoV-2 infection:
  - On humoral immune response
  - On measures of infectivity of SARS-CoV-2 as assessed in experimental laboratory assays
- To explore the relationships between REGN10933+REGN10987 exposure and selected clinical efficacy and safety endpoints and/or biomarkers in seropositive and seronegative subjects
- To assess viral genetic variation in SARS-CoV-2 in subjects with a positive SARS-CoV-2 RT-qPCR.
- To explore biomarkers (including host genome variants) associated with safety and efficacy of REGN10933+REGN10987 and to study SARS-CoV-2

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline

Prophylaxis with SC administration of anti-spike REGN10933+REGN10987 will:

1. Prevent the occurrence of symptomatic infection with SARS-CoV-2.
2. Prevent the occurrence of asymptomatic and symptomatic infection with SARS-CoV-2.

3. Be well-tolerated.

Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline

Preemptive therapy with SC administration of REGN10933+REGN10987 will:

1. Prevent the development of symptomatic SARS-CoV-2 infection in household contacts who already have a positive SARS-CoV-2 RT-qPCR test at baseline
2. Be well-tolerated.

3.2. Rationale

3.2.1. Study Design

This randomized, double-blind, placebo-controlled, phase 3 study will assess the safety, tolerability, and efficacy of REGN10933+REGN10987 in adult subjects and pediatric subjects (<18 years of age) who are household contacts of the first known household member infected with SARS-CoV-2 (index case). Collection of clinical and virologic data using a standardized timeline will provide valuable information on the clinical course of SARS-CoV-2 infection and the impact of these mAbs to prevent infection and symptomatic disease associated with SARS-CoV-2. The multicenter conduct of this study will enable generalizable evidence of the safety, tolerability, and efficacy of investigational mAbs. Specifically, this study is intended to demonstrate the efficacy of REGN10933+REGN10987 to prevent SARS-CoV-2 infection (with or without symptoms) in uninfected subjects or prevent symptomatic disease (eg, preemptive therapy) in subjects already infected (ie, SARS-CoV-2 RT-qPCR positive) at baseline. The double-blind design serves to reduce potential bias introduced by knowing the study drug assignment. The comparator arm in this study will be placebo as no approved preventative treatments are currently available. The placebo arm will also provide an estimate of the background incidence of SARS-CoV-2 infection and disease, as well as of adverse event (AE) rates for both efficacy and safety analyses. Additionally, all subjects' SARS-CoV-2 serology status, including baseline, will also remain blinded to study site personnel during the study to avoid potential bias introduced when evaluating and assessing subjects who are seropositive and to mitigate the possibility of less risk averse behaviors in which subjects might engage. The study size and duration were driven by current epidemiological assumptions about study population and are detailed in Section 11.2.

This study was preceded by safety review of data from other studies: a safety sentinel group of 30 adult patients with COVID-19 dosed with REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 8000 mg IV or placebo in the leading phase 1 studies of REGN10933+REGN10987 in the treatment of COVID-19 patients. Randomization in this study began when the Independent Data Monitoring Committee (IDMC) for the treatment studies provided a "study may proceed" conclusion from the IV dosing sentinel group (Section 3.2.4).

All subjects in the study will be household contacts of the first known household member to be infected with SARS-CoV-2 (index case) but who are themselves ***asymptomatic*** (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening. Randomization will be performed on an individual subject basis rather than by household, however all subjects randomized will be given a household identification number in the case that multiple members of the same household are enrolled and receive study drug. This ensures that correlation among subjects within the same household may be considered in the statistical analysis. Some of the household members of the study subjects in this study may receive EUA approved monoclonal antibody treatment for COVID-19 or may be participating in a separate treatment study assessing the efficacy of REGN10933+REGN10987 in outpatients with COVID-19 (study R10933-10987-COV-2067). Therefore, EUA monoclonal antibody treatment of household members, as well as information from R10933-10987-COV-2067 and R10933-10987-COV-2069 studies will be linked, where applicable, to assess the impact of monoclonal antibody treatment of the COVID-19 infected household members on infectivity of study subjects.

The study will consist of a screening/baseline period that will occur on the same day, due to the short window (96 hours) between the collection of the index cases' positive SARS-COV-2 diagnostic test sample and randomization of the study subject(s). This same day screening/baseline period is expected to decrease the burden of study visits on the subject and might help to increase subject engagement. For the same reason, only a subset of subjects (by subject ordinal number as first subjects are randomized using the interactive web response system [IWRS]) will undergo PK and intensive safety laboratory testing throughout the study (approximately 30 subjects for dense PK sampling, approximately 400 subjects for sparse PK sampling, and intensive safety laboratory assessments). The number of subjects selected for PK sampling and for intensive safety lab assessments are considered sufficient to provide an adequate evaluation of the different parameters.

At the screening/baseline visit, subjects will have a local, diagnostic assay for SARS-CoV-2 from appropriate samples. The results of this local test will be used as a stratification factor for randomization for assigning subjects into 1 of 2 treatment groups. In the event that local testing result is not anticipated to be available in the time required during screening, subjects may be randomized (local test will be specified as "undetermined" in IRT). Subjects will also have NP swab samples collected at baseline for central lab SARS-CoV-2 RT-qPCR tests. The results of the central lab RT-qPCR (the results of which may not be available on the same day due to time for shipping) will be used for cohort allocation into cohort A and cohort A1 (negative) or cohort B and cohort B1 (positive) for data analysis.

Within this study, a sentinel safety group that consisted of the first 30 adult subjects who completed day 4 safety assessments was assessed. Subjects were observed at the study site for 4 hours after the single-dose SC study drug administration and were specifically monitored for acute hypersensitivity reactions or injection site reactions, which constitute the primary potential risks with SC injection of a fully human monoclonal antibody against an exogenous target. Subjects were then assessed daily for the first 4 days after study drug administration for evaluation of treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESI). Blinded safety data was reviewed before progressing with enrollment of additional study subjects. This close observation of the first 30 subjects was considered sufficient to assess safety and allow further enrollment of study subjects as the risk for AEs or AESIs is highest during the first days following study drug administration. This sentinel safety monitoring was considered adequate because REGN10933+REGN10987 was already cleared by a sentinel safety group who received higher doses (2400 mg and 8000 mg) administered IV.

The Blinded Safety Data for the R10933-10987-COV-2069/COVID-19 Prevention Network (CoVPN) 3502 study was reviewed and the monitoring team met via teleconference on 04 Aug 2020 to discuss the sentinel data.

After review of the totality of evidence the Blinded Safety Data Review team found no reasons to recommend alteration or termination of the study. Study R10933-10987-COV-2069/CoVPN 3502 can continue enrolment as planned per protocol.

Available clinical safety data (including adverse experiences, AESIs, injection site reactions and hypersensitivity reactions, vital signs, and safety labs) from the first 30 subjects who received a single dose of 600mg REGN10933+600mg REGN10987 SC or matching placebo SC and who completed safety assessment visits through day 4 were reviewed. Also, laboratory results available to date were reviewed including samples collected through day 2 for 27 subjects, and samples collected through day 4 for 18 subjects. Neither SAEs, nor AESIs were reported among the 30 subjects. No reported injection site reactions or hypersensitivity reactions occurred among the 30 subjects. There were 12 TEAEs reported in 7 subjects, all grade ≤2. No TEAEs were deemed related to study drug. There were no patterns of clinically concerning changes in vital signs or safety laboratory parameters among 600mg REGN10933+600mg REGN10987/placebo treated subjects. In summary, treatment with 600mg REGN10933+600mg REGN10987/placebo when administered as a single SC dose was sufficiently well tolerated to warrant continued enrolment as planned per protocol.

Inclusion of Subjects Under 18 years of Age and Pregnant and Breastfeeding Women

Adolescent subjects (12 to <18 years) enrollment was initiated in this study because this population is vulnerable to infection with SARS-CoV-2 in the household (Lewis, 2020), and REGN10933+REGN10987 appears well tolerated in adults, with over 1000 adult subjects having already received REGN10933+REGN10987, either in the treatment studies (single dose of 2400 mg intravenous (IV) or 8000 mg IV [R10933-10987-COV-2066, R10933-10987-COV-2067]), or the prophylaxis study (1200 mg subcutaneous (SC) as a single dose [R10933-10987-COV-2069]), or the healthy subject safety study (1200 mg SC as multiple doses every 4 weeks (Q4W) for 6 doses [R10933-10987-COV-2093]). Upon review of safety data from approximately the first 20 adolescent subjects (≥12 to <18 years of age) enrolled, pediatric subjects aged birth to <12 years of age will also be enrolled. The pediatric subjects will be analyzed as separate cohorts (cohort A1 and cohort B1) to assess the safety, PK, immunogenicity, and efficacy of REGN10933+REGN10987.

Pregnant women and breastfeeding women are being included in this study because pregnant women are at increased risk of developing severe COVID-19 (Ellington, 2020) (Knight, 2020)(Woodworth, 2020). The risks of REGN10933+REGN10987 treatment for pregnancy and a developing fetus are unknown. Because REGN10933+REGN10987 mAbs are directed against an exogenous antigen, administration of REGN10933+REGN10987 is not anticipated to affect endogenous pathways. Addition of pregnant women to the study is also supported by the results of nonclinical studies that show no changes to reproductive organs in nonhuman primates and an absence of human tissue cross reactivity with REGN10933 or REGN10987 in human or monkey tissues evaluated (see the IB). Because pregnant women are allowed in the study, contraception for women of childbearing potential (WOCBP) is no longer required as an exclusion criterion; however, all WOCBP will undergo pregnancy testing prior to dosing and at the end of study. Women who are pregnant or who become pregnant during the study will be followed for the outcome of their pregnancy. Also, because pregnant women are allowed in the study, contraception for men is no longer required as an exclusion criterion. We will not solicit information regarding pregnancies occurring in the female partners of male study subjects as the risk of exposure is negligible in this scenario. The safety profile in pediatric subjects <12 years and pregnant and breastfeeding women is expected to be similar to that observed in adults and adolescents. Safety data is reviewed in a continuous manner by the sponsor (blinded data) and by the Data and Safety Monitoring Board (DSMB) (unblinded data).

The study has a 28-day efficacy assessment period (EAP) after the single dose of active study drug or placebo administered SC to capture all infections as detected by SARS-CoV-2 RT-qPCR positivity (both asymptomatic and symptomatic), symptomatic infection (ie, those individuals that experience symptoms consistent with SARS-CoV-2 infection and progression of COVID-19 disease). A 28-day assessment period is expected to be sufficient to accrue an adequate number of primary endpoint events within the planned sample size. The incubation period of SARS-CoV-2 after exposure is approximately 2 to 14 days (Li, 2020a) (Lauer, 2020). The duration of mild to moderate symptoms, including time to hospitalization, is approximately 11.5±5.7 days (Lechien, 2020). Following the 28-day EAP, subjects will undergo a 7-month follow-up period to assess for TEAEs, PK, and anti-drug antibodies (ADA) and neutralizing antibodies (NAbs). This duration is based on a half-life of 21-days for a typical mAb. This follow-up period is expected to allow an assessment of safety after discontinuing treatment. The length of the follow-up period may be modified based on the observed PK and ongoing nonclinical data as it becomes available. The occurrence and severity of any suspected COVID-19 related AEs (including SAEs) that occur as drug concentrations wane will be monitored, and subjects who received active drug or placebo will be assessed for any signal of ADE.

3.2.2. Subject Population

The study population will consist of approximately 3500 adult and adolescent subjects and approximately 250 pediatric subjects <12 years old, with household contact exposure to individual with a confirmed SARS-CoV-2 infection. In this study, the household contact must share the same residence and have a close exposure to the first individual in the household with a known SARS-CoV-2 infection (index case). In the case where more than 1 index case is the first known SARS-CoV-2 infected individual in the household (eg, 2 people are tested at the same time), this is allowed, and 1 index case should be chosen, at the discretion of the investigator, to be labeled "index case" in the household CRF. The study was originally planned to enroll 2000 adult and adolescent subjects. However, a blinded analysis of approximately 25% of enrolled subjects in this study was performed, demonstrating that higher than expected seropositivity was observed in cohort A. Therefore amendment 4 for the protocol increased the sample size for the study to account for the higher than expected seropositivity in cohort A. Amendment 5 for the protocol increased the sample size further to accommodate the administrative assessment of assumption verification and sample size estimation.

A household is defined as a group of people who live together at the same residence and share multiple living spaces (eg, living room, bedroom, kitchen, bathroom). In case there is uncertainty that the characteristics of the residence meets the definition of a 'household', the investigator and the Regeneron Medical Monitor should discuss prior to randomization.

To be included in the study, subjects must be randomized within 96 hours of collection of the index cases' positive SARS-COV-2 diagnostic test sample. Household contacts of individuals infected with SARS-CoV-2 are at a high risk for acquiring infection, with transmission rates ranging from approximately 10% to 15% in these settings (Burke, 2020) (Jing, 2020) (Li, 2020b). Therefore, approximately 15% of subjects were expected to develop symptomatic disease in follow-up after a household contact transmission event (Li, 2020b). A minority of subjects were expected to be seropositive at baseline, as seropositivity in the general population, outside of hard-hit areas like New York City, was expected to be less than 10% (Burke, 2020). Upon blinded review of approximately the first 25% of subjects enrolled into this study, baseline seropositivity rates in cohort A subjects were approximately 3 times higher than anticipated and a minority of cohort A subjects who became infected during the 28 day efficacy assessment period were symptomatic. Subjects with positive rapid SARS-CoV-2 RT-PCR at the time of randomization, who are either seronegative or seropositive at baseline will also be included in the study, but only subjects who are both seronegative and negative for SARS-CoV-2 infection by central lab RT-qPCR at baseline will be included in the primary efficacy analysis.

3.2.3. Enrollment by Baseline SARS-CoV-2 Infection

This study will include asymptomatic subjects regardless of baseline SARS-CoV-2 infection status or serologic status. Including all-comers into the study will provide important information on infection prevention through prophylaxis as well as the impact of pre-emptive therapy in infected but asymptomatic individuals. Since the primary efficacy objective in cohort A is focused on the prevention of symptomatic SARS-CoV-2 infection (broad-term), the primary population of interest are subjects that are seronegative and SARS-CoV-2 RT-PCR negative at baseline. It was estimated that approximately 10% of the study population for cohort A would be seropositive at baseline. However, blinded data review of approximately the first 25% of subjects enrolled shows that approximately 30% of subjects in cohort A are seropositive at baseline. Therefore, the majority of subjects enrolled are expected to be allocated to the primary study population of interest, seronegative and SARS-CoV-2 RT-PCR negative at baseline (ie, cohort A).

On day 1 and prior to randomization, subjects will have a local diagnostic assay for SARS-CoV-2 from an appropriate sample. Samples will also be collected for central lab SARS-CoV-2 RT-qPCR and serology tests. The results of the local lab tests will be available the same day and will be used as stratification for randomization to allow administration of study drug. In the event that local testing results are not anticipated to be available in the time required during screening, subjects may be randomized.

For data analysis, adult and adolescent subjects will be divided into 2 independent study cohorts: cohort A or cohort B. This allocation will be based on a central lab SARS-CoV-2 RT-qPCR test result performed during the screening/baseline visit. While stratification and randomization will be based on local test results, data analyses will be based on the central lab results of baseline SARS-CoV-2 RT-qPCR results from NP swab sample and the serological status.

The analysis of the adult and adolescent subject populations that are not part of the primary study population of interest (ie, those subjects in cohort A who are seropositive at baseline) will not contribute to a primary study objective or endpoint. These individuals will be analyzed separately either through secondary or exploratory objectives and endpoints.

Adult and adolescent subjects in cohort B (ie, asymptomatic subjects who are SARS-CoV-2 RT-qPCR positive at baseline, irrespective of the serology status being positive or negative) will be analyzed separately from cohort A with a primary study objective and endpoint, secondary and exploratory objectives and endpoints. The primary efficacy objective in cohort B is focused on the prevention of COVID-19 symptoms (broad-term) in the subjects who are seronegative but

SARS-CoV-2 RT-qPCR positive at baseline. The analysis of the adult and adolescent subject populations that are not part of the primary study population of interest (ie, those subjects in cohort B who are seropositive at baseline) will not contribute to a primary study objective or endpoint. These individuals will be analyzed separately either through secondary or exploratory objectives and endpoints.

Pediatric subjects (<12 years) will be divided into 2 independent study cohorts, cohort A1 or cohort B1. This allocation will be based on a central lab SARS-CoV-2 RT-qPCR test result performed during the screening/baseline visit.

To mitigate enrollment of a high percentage of subjects that are either seropositive or SARS-CoV-2 RT-qPCR positive at baseline, those with a known prior history of a positive SARS-CoV-2 RT PCR test, a positive serology test, or COVID-19 will be excluded.

All subjects' SARS-CoV-2 qualitative diagnostic and RT-qPCR test results will be unblinded during the study. This will ensure SARS-CoV-2 infected individuals take the appropriate precautions necessary to prevent spread of disease. However, all subjects' SARS-CoV-2 serology results will remain blinded to study site personnel during the study to avoid potential bias introduced when evaluating and assessing subjects who are seropositive and to avoid encouraging higher risk behaviors through disclosure of seropositivity.

3.2.4. Sentinel Safety Group and Subsequent Safety Reviews

Driven by the medical urgency of the COVID-19 pandemic, the process described below is designed to maximize efficient enrollment of eligible subjects while optimizing the safety of the first SC administration of REGN10933+REGN10987. Clinical safety and tolerability data from the pooled sentinel cohorts from treatment studies (R10933-10987-COV-2066 and R10933-10987-COV-2067) in COVID-19 patients receiving IV administration of REGN10933+REGN10987 were available prior to first SC dosing in this study.

A safety review of data from an adult sentinel safety group was conducted by the unblinded IDMC/DSMB as a precondition for further enrollment across the REGN10933+REGN10987 clinical development program. The sentinel group consisted of 30 subjects pooled across the 2 treatment studies of REGN10933+REGN10987 administered as a single IV dose in patients with COVID-19 (R10933-10987-COV-2066 and R10933-10987-COV-2067). Patients in this sentinel group were randomized to receive a single IV dose of REGN10933+REGN10987 (at 1200 mg per mAb, at 4000 mg per mAb), or placebo. The IDMC/DSMB approved the continuation of the treatment studies and the initiation of the prophylaxis study. Additionally, a blinded Sponsor analysis of the adult treatment study data showed that REGN10933+REGN10987 was sufficiently well-tolerated to warrant continued enrollment as planned per protocol, with no hypersensitivity reactions or infusion-related reactions reported. Vital signs, and laboratory assessments did not identify any safety signals.

The description of the sentinel groups, safety monitoring of sentinel subjects (adult and pediatric [<12 years]), and data review for this study is provided in Section 6.1.1 and Section 6.1.2.

A blinded Sponsor analysis of the sentinel data for adult subjects in this study (R10933-10987-COV-2069) showed that REGN10933+REGN10987 was well-tolerated, with no hypersensitivity reactions or injection site reactions reported. The continuous review of blinded safety data for the study, eg, AEs, vital signs, and laboratory assessments, have not identified any safety signals.

3.2.5. Primary Objective

The primary objectives of this study are:

- Cohort A: To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR in asymptomatic subjects at risk who are seronegative at baseline.
- Cohort B: To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing COVID-19 symptoms (broad-term) in asymptomatic subjects that are SARS-CoV-2 RT-qPCR positive and seronegative at baseline.

The FDA Guidance on COVID-19 recommends that in prevention trials, the primary endpoint should be the occurrence of laboratory-confirmed SARS-CoV-2 infection, with or without symptoms. A descriptive administrative analysis of seronegative subjects in cohort A (n=409) demonstrated a 100% reduction in broad-term symptomatic PCR-positive infection with 8/223 (3.6%) placebo treated subjects developing symptomatic infection versus 0/186 (0%) REGN10933+REGN10987 treated subjects; OR 0.00 (0.00, 0.69) $p<0.01$. The revised primary objectives and endpoints for cohort A are informed by these results. Thus, these revisions are applied to objectives and endpoints for cohort B as well. The final primary objectives and endpoints for the completed study will be assessed in the final study population enrolled, excluding those that were already unblinded and assessed in the descriptive administrative analysis (Section 11.4.9). Protocol amendment 6 specifies a single primary objective and endpoint for each cohort which consists of the prevention of laboratory confirmed symptomatic SARS-CoV-2 infection (broad term)(Section 2.1.1.1 and Section 4.1.1).

Clinical efficacy: The ability of REGN10933+REGN10987 administration to prevent symptomatic SARS-CoV-2 infection (broad-term) will be evaluated through weekly inquiry by the investigator to assess if subjects experienced or are experiencing commonly reported clinical signs/symptoms related to COVID-19. A broad definition of signs/symptoms associated with COVID-19 (see Section 9.2.2.2 for full definition) will be utilized for the primary endpoint. Commonly reported symptoms of COVID-19 include fever, cough and myalgias. However, SARS-CoV-2 infection has been associated with a wide variety of symptoms (eg, loss of taste and smell). In order to ensure all symptomatic SARS-CoV-2 infections are captured during the study, a broad term definition of any one of 23 symptoms will be reported by the investigator in association with a laboratory confirmed SARS-CoV-2 infection (see Section 9.2.2.2).

3.2.6. Secondary Objectives

The secondary objectives and endpoints are informed by results of the descriptive administrative analysis and include the assessment of laboratory confirmed SARS-CoV-2 infection with or without symptoms (strict term and CDC definition as described below), the magnitude and duration of laboratory confirmed infection, and the impact of treating a COVID-19 infected household member with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection.

Clinical efficacy: While the primary objective captures symptomatic infections defined by a broad-term, secondary objectives include both a more strict definition of signs/symptoms associated with COVID-19 and the CDC definition (see Section 9.2.2.2 for full definitions). Other secondary objectives will assess important clinical outcome measures including healthcare utilization (seeking an emergency room or urgent care facility, hospitalization, length of hospital stay, etc), the duration of disease in subjects who develop symptomatic infection, and the impact of index case treatment with REGN10933+REGN10987 on infection events in the study subject in this study. Similar objectives will be applied to subjects who are SARS-CoV-2 RT-PCR positive and/or seropositive at baseline (CDC, 2020b).

Virologic efficacy: The primary mechanism of action of REGN10933+REGN10987 is blockade of the S protein RBD interaction with ACE2, leading to inhibition of SARS-CoV-2 host cell infection. The ability of REGN10933+REGN10987 treatment to prevent SARS-CoV-2 infection will be evaluated by SARS-CoV-2 RT-qPCR test results from weekly NP swab samples. Weekly sample collection is considered an adequate collection frequency to ensure early detection of viral load (SARS-COV-2 RT-qPCR positivity) in infected individuals; this is based on the average duration of viral positivity from NP swabs that ranges from 7 to 28 days (He, 2020) (Wölfel, 2020). All subjects will have SARS-CoV-2 RT-qPCR testing by NP sample. Nasopharyngeal swab testing has been shown to have good sensitivity and specificity for detecting SARS-CoV-2 RNA (Zou, 2020) (Pere, 2020). The administrative assessment of seronegative subjects (n=409) in cohort A demonstrated that the risk of becoming infected (ie, becoming SARS-CoV-2 RT-PCR positive) was reduced as early as the first week of study (10.3% in subjects in the placebo group versus 5.4% in subjects in the REGN10933+REGN10987 group at day 8). The protection continued through the following weeks. Both the magnitude and duration of infection were reduced by REGN10933+REGN10987 treatment. Infections occurring in subjects in the placebo group had, on average, more than 100-fold higher peak viral load. Infections in subjects in the REGN10933+REGN10987 group lasted no more than 1 week, while approximately 40% of infections in subjects in the placebo group lasted 3 to 4 weeks. No infected subjects in the REGN10933+REGN10987 group had high viral loads (>10^4 copies/mL) compared to 62% of the infected subjects in the placebo group (13/21 placebo versus 0/9 REGN10933+REGN10987) (CDC, 2020b). (CDC, 2020b)

3.2.7. Rationale for Dose Selection

This study will assess a single SC dose of REGN10933+REGN10987 as combination therapy in a 1:1 ratio. The 1:1 ratio for REGN10933+REGN10987 is thought to be appropriate as these are noncompeting mAbs targeting non-overlapping epitopes of the RBD of the S protein of SARS-CoV-2, with similar in vitro binding and neutralization properties (for more information, refer to the IB). The study will evaluate REGN10933+REGN10987 as combination therapy at a 1200 mg (600 mg of each mAb) SC dose.

Angiotensin converting enzyme subtype 2 expression has been reported in the lungs, particularly in type-2 alveolar epithelial cells and bronchial airway epithelium (Wu, 2020) (Xu, 2020) (Zhao, 2020). The strategy taken for dose selection in this study was to identify a target concentration in lung epithelial lining fluid (ELF) that approximates the effective concentration required for 99% neutralization (EC_{99}) of SARS-CoV-2 in vitro and to then identify a dose that will meet or exceed this concentration in lung ELF. The EC_{99} against SARS-CoV-2 in vitro is 0.14 µg/mL for REGN10933 and 0.80 µg/mL for REGN10987.

An average lung ELF-to-serum mean C_{max} ratio of ~0.15 has been reported for other exogenous IgG1 mAbs for the treatment of Staphylococcus aureus lung infections (Magyarics, 2019). It is assumed that the lung ELF-to-serum C_{max} ratio is 0.15 for REGN10933 and REGN10987. Dividing the target lung ELF concentration by this ratio, the associated serum concentration for these targets is therefore estimated to be ~at least 5 µg/mL for the combination of REGN10987+REGN10933.

Taking into account uncertainties regarding mAb penetration into lung ELF, prediction of human PK, and effects of disease on PK, 20 µg/mL was selected as a target concentration in serum for subjects using the 600 mg SC per mAb REGN10933+REGN10987 combination dose. The goal for this REGN10933+REGN10987 combination dose is for ≥95% of subjects to exceed the target serum concentration for 28 days after dosing. To estimate the clinical SC dose required to achieve this goal, a population PK model developed for a typical Regeneron mAb administered SC was used to simulate mean and 5th percentile serum concentrations for a virtual population of 2000 subjects (mean (SD) [min, max] body weight of 85 (17) [40, 150] kg) for various SC doses.

For a single 600 mg per mAb SC dose, ≥95% of adult subjects are predicted to exceed the target serum concentration by approximately 1 day after the first dose and remain above the target serum concentration for the remainder of the 28-day treatment period, for each mAb.

As the lower end of the proposed body weight range for adolescent subjects ≥12 years of age (40 kg) falls within the range of expected body weights for adult subjects, similar exposures are expected between these 2 populations for a single 1200 mg (600 mg of each mAb) SC dose of REGN10933+REGN10987.

Similar to adults, the goal for dose selection in the pediatric population is for ≥95% of pediatric subjects within each weight-tiered group to exceed the 20 µg/mL target concentration in serum per mAb for 28 days after dosing. An additional consideration was to select doses for pediatric subjects that would achieve exposures within the range of those shown to be generally safe and well tolerated in adults.

The same 2-compartment population PK model with linear clearance developed for adults was used to simulate concentrations in serum over time for various doses in each pediatric weight-tiered group using allometrically scaled estimates of clearance and volume of distribution (gestational-age corrected allometrically scaled estimates were used for subjects <10 kg) (Robbie, 2012). The doses selected are predicted to result in ≥95% of subjects within each weight tier exceeding the 20 µg/mL target concentration in serum per mAb for 28 days after dosing (Table 1). Compared to predicted 95th percentiles of C_{max} and AUC_{0-28} for REGN10933 and REGN10987 in adults after a single SC dose of 1200 mg (600 mg per mAb), the 95th percentiles of predicted C_{max} and AUC_{0-28} across the different pediatric weight-tiered groups ranged from 18% to 88% higher than in adults, but lower than observed mean C_{max} and AUC_{0-28} values for the lowest single IV dose (2.4 g) with an acceptable safety profile in adults with COVID-19. For children < 10 kg, SC administration is not deemed feasible, and it is assumed that the concentration-time profile of REGN10933 and REGN10987 will be similar for intramuscular (IM) and SC administration.

Table 1: REGN10933+REGN10987 Doses for Each Pediatric Weight-Tiered Groups

Pediatric Weight-Tiered Groups	Route of Administration	Dose (mg)		Total Dose (mg)
		REGN10933	REGN10987	

≥40 kg	SC	600	600	1200
≥20 to <40 kg	SC	396	396	792
≥10 to <20 kg	SC	204	204	408
≥5 to <10 kg	IM	72	72	144
≥2.5 to <5 kg	IM	48	48	96
<2.5 kg	IM	24	24	48

A 4-week GLP toxicology study in cynomolgus monkeys was conducted and assessed once weekly dosing of up to 150/150 mg/kg per mAb administered once weekly (for combination) to support safety of the anti-SARS-CoV-2 spike mAbs. Throughout the 4-week dosing period the REGN10933+REGN10987 combination was well tolerated at all dose levels, with no drug-related or adverse effects evident (for more information, refer to the IB).

3.3. Risk-Benefit

This study represents the initial prophylaxis study planned to evaluate REGN10933+REGN10987 as a SC injection in humans. Therefore, the potential clinical benefits and risks associated with the study drugs are yet to be determined. Several preclinical pharmacokinetic, pharmacologic, and toxicology studies are ongoing and/or planned, and findings from these studies will be appropriately communicated. While preclinical data are available (discussed below), the anticipated risks are based primarily on prior Sponsor experience with similar fully human monoclonal antibody development programs against exogenous targets and the potential risks associated with subcutaneous injection of fully human monoclonal antibodies in general.

The positive efficacy results observed for REGN10933+REGN10987 administered IV to symptomatic patients with COVID-19 in R10933-10987-COV-2067 study are balanced by an acceptable safety profile. Nonclinical toxicology studies in nonhuman primates showed that REGN10933+REGN10987 was well-tolerated without adverse findings. Moreover, review of available clinical data from the 3 ongoing clinical studies (R10933-10987-COV-2066, R10933-10987-COV-2067, R10933+REGN10987-HV-2093) show that there are currently no identified risks with REGN10933+REGN10987. There are several potential risks, which are described below.

A 4-week GLP toxicology study in cynomolgus monkeys is currently ongoing and assessing once-weekly IV and SC dosing of REGN10933+REGN10987 at up to 150 mg/kg per antibody. Findings from the completed 4-week dosing period of the toxicology study identified no clinically relevant risks or test article-related adverse effects and no changes to reproductive organs in nonhuman primates. Separately, findings from 2 tissue cross reactivity studies was notable for by the absence of any tissue cross reactivity with either REGN10933 or REGN10987 in any of the human or monkey tissues or human fetal tissues evaluated. Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy on the fetus and reproductive organs in males and females are unknown.

REGN10933 and REGN10987 target the SARS-CoV-2 S protein, an exogenous protein. The Sponsor has significant experience with prior development programs for fully human mAbs against exogenous targets, including atoltivimab, odesivimab, and maftivimab (Ebola), REGN3048 and REGN3051 (MERS-CoV), REGN5713, REGN5714 and REGN5715 (Bet v 1 birch tree allergen), and REGN1908 and REGN1909 (Fel d 1 cat dander allergen). No significant safety findings were observed in any of the associated toxicology studies conducted and the mAbs demonstrated an acceptable safety profile in the clinical studies.

Important Potential Risks: The important potential risks are those typically associated with a mAb administered by SC route: injection site reactions, hypersensitivity reactions, immunogenicity, and potential embryo-fetal toxicity (see the IB). REGN10933 and REGN10987 are fully human IgG1 mAbs, and correspondingly the risk of injection site reactions, hypersensitivity reactions, or immunogenicity is expected to be low. However, given the limited experience with these mAbs and the evolving understanding of SARS-CoV-2 infections, all TEAEs will be collected during the study to adequately characterize the safety profile of REGN10933+REGN10987. Clinical safety and tolerability data from the pooled sentinel cohorts from treatment studies (R10933-10987-COV-2066 and R10933-10987-COV-2067) in COVID-19 patients receiving IV administration of REGN10933+REGN10987 were available prior to first SC dosing in this study. These data showed that a single IV dose of REGN10933+REGN10987 or placebo (at 1200 mg per mAb, at 4000 mg per mAb) was well-tolerated, with no hypersensitivity reactions or infusion-related reactions reported. Vital signs and laboratory assessments did not identify any safety signals (Section 3.2.4). Protein therapeutics carry the potential risk of an immunogenic response in the form of ADA and NAb development following administration, with possible consequences on safety and efficacy. Therefore, blood samples for immunogenicity assessment will be collected during the studies.

Reproductive and developmental toxicology studies have not been conducted; therefore, the effects of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy on the fetus and reproductive organs in males and females are unknown. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier and are present in breast milk; therefore, the REGN10933+REGN10987 combination therapy have the potential to be transferred from the mother to the developing fetus or a breastfed child. Given the high affinity and specificity of REGN10933 and REGN10987, off-target pharmacological effects are not anticipated in either the mother, the fetus, or breastfed child and no off-target binding of REGN10933 or REGN10987 was observed in any of the human or monkey tissues evaluated ex vivo in tissue cross-reactivity studies. However, it is unknown whether the potential transfer of the combination of REGN10933+REGN10987 therapy provides any treatment benefit or risk to the developing fetus or breastfed child.

There is currently limited clinical experience in the use of REGN10933, REGN10987, and REGN10933+REGN10987 combination therapy in female subjects who are pregnant or breastfeeding. The combination of REGN10933+REGN10987 therapy should be used during pregnancy or breastfeeding only if the potential benefit justifies the potential risk for the mother and the fetus or breastfed child considering all associated health factors. If a female subject is pregnant or were to become pregnant while receiving REGN10933+REGN10987 combination, the pregnancy should be followed until outcome and any safety issue observed get reported.

Other Theoretical Considerations: Antibody-dependent enhancement (ADE) has also been observed for some therapeutics targeting exogenous viral proteins. For antibody therapies, ADE is thought to occur when binding of antibody to the target viral protein enhances FcγR-mediated host cell entry of the virus (Iwasaki, 2020). This could potentially lead to worsening of disease and, in the case of SARS, acute lung injury (Liu, 2019). REGN10933 and REGN10987 retain the Fc region, as this may play a role in protecting against viral infection (Yasui, 2014). However, there is no strong evidence of ADE in other coronavirus models (Kam, 2007) (Liu, 2019) (Luo, 2018) (Wang, 2016) (Weingartl, 2004). To date, Fc-containing mAbs developed by the Sponsor for Ebola virus, and MERS-CoV have demonstrated specificity to their exogenous targets with no significant unexpected safety findings in preclinical or clinical studies. All subjects will be monitored for TEAEs during the drug elimination period. Theoretical risks of administration of the REGN10933+REGN10987 combination include interference with the subject's endogenous immune response to either SARS-CoV-2 infection or vaccination against SARS-CoV-2.

With respect to efficacy, the currently available in vitro data (see the IB) show that REGN10933+REGN10987 is anticipated to be pharmacologically active at the planned dose, with expected neutralization and effector functions against the SARS-CoV-2 S protein. Additionally, the only control measures that are currently available against this virus is practicing rigorous infection control. There is no therapeutic option for the prevention of SARS-CoV-2 infection and there is an urgent need for a preventative treatment given the wide reaching, devastating effects of this global outbreak (Woodworth, 2020).

Emerging data suggest that the pediatric population is equally vulnerable to SARS-COV-2 infection and may contribute significantly to transmission (Szablewski, 2020) (Lewis, 2020) (Viner, 2020)and that pregnant women are at increased risk for developing severe COVID-19 and have been shown to have a higher rate of hospitalization, need for mechanical ventilation, and ICU admission than non-pregnant women (Ellington, 2020) (Knight, 2020)(Woodworth, 2020). Neonatal transmission of SARS-CoV-2 has also been reported (Vivanti, 2020). Therefore, all adults and children should be considered for inclusion in COVID-19 prophylaxis efforts.

In summary, based on prior experience with other fully human mAbs against exogenous targets, the available clinical and nonclinical data for REGN10933+REGN10987 to date, and the unmet need for a preventative therapy in advance of an approved vaccine, it is the opinion of the Sponsor that the overall risk-benefit balance for REGN10933+REGN10987 is acceptable to allow evaluation of this mAb combination in all populations, including adults, pregnant and breastfeeding women, and children who are household contacts of an infected individual and therefore at high risk for SARS-CoV-2 infection.

For more details, refer to the IB.

4. ENDPOINTS

Endpoints are specified for study cohorts (as defined in Section 6.1.6).

Symptomatic SARS-CoV-2 infection is determined by a positive central lab SARS-CoV-2 RT-qPCR result during the EAP with signs/symptoms occurring within ±14 days of a positive RT-qPCR.

The "strict-term", "broad-term" and CDC definitions for signs/symptoms of SARS-CoV-2 infection is presented in Section 9.2.2.2.

4.1. Cohort A and Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline

The endpoints are for subjects who are seronegative at baseline (based on central lab test), unless stated otherwise.

4.1.1. Cohort A Primary Endpoints

Cohort A Primary Efficacy Endpoint

- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP

Cohort A and Cohort A1 Primary Safety Endpoints

- Proportion of subjects with TEAEs and severity of TEAEs

4.1.2. Cohort A Key Secondary Endpoints

- Proportion of subjects with viral load >4 ($\log_{10}$ copies/mL) in NP swab samples during the EAP
- Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
- Number of weeks of high viral load >4 ($\log_{10}$ copies/mL) in NP swab samples during the EAP
- Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
- Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 versus placebo in study R1033-10987-COV-2067)

4.1.3. Cohort A and Cohort A1 Other Secondary Endpoints

- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (CDC definition) during the EAP
- Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (CDC definition) during the EAP
- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (strict-term) during the EAP
- Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (strict-term) during the EAP

- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection at each week in the EAP
- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad term) at each week in the EAP
- Time-weighted average of viral load ($\log_{10}$ copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the third weekly visit after the first positive test during the EAP *(Note: Only for RT-qPCR positive subjects during the EAP in the seronegative modified full analysis set for cohort A [seronegative mFAS-A])*
- Time-weighted average of viral load ($\log_{10}$ copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the second weekly visit after the first positive test during the EAP *(Note: Only for RT-qPCR positive subjects during the EAP in the seronegative mFAS-A*
- Maximum SARS-CoV-2 RT-qPCR viral load ($\log_{10}$ copies/mL) in NP swab samples among individuals with ≥1 RT-qPCR positive that has an onset during the EAP
- SARS-CoV-2 RT-qPCR viral load ($\log_{10}$ copies/mL) in NP swab samples corresponding to the onset of first positive RT-qPCR during the EAP
- Area under the curve (AUC) in viral load ($\log_{10}$ copies/mL) from the first positive SARS-CoV-2 RT-qPCR NP swab samples detected during the EAP until the first confirmed negative test (testing that occurs after the EAP will be included if necessary to achieve a negative test result) *(Note: Only for RT-qPCR positive subjects during the EAP in the seronegative mFAS-A)*
- Number of medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Proportion of subjects with at least 1 COVID-19-related hospitalization or emergency room visit associated with a positive RT-qPCR during the EAP, or all-cause death
- Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Number of days of hospital and intensive care unit (ICU) stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (students), daycare or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP
- Proportion of subjects in the placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with at least 1 household member participating either in study R10933-10987-COV-2067 or in cohort B (comparison of those whose households

members receive REGN10933+REGN10987 versus placebo in study R1033-10987-COV-2067 or in cohort B)

Additional Cohort A1 Secondary Efficacy Endpoint

- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP.
- Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP
- Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
- Number of weeks of high-viral load >4 (log10 copies/mL) in NP swab samples during the EAP
- Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
- Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 versus placebo in study R1033-10987-COV-2067)

Cohort A and Cohort A1 Safety Endpoints

- Proportion of baseline seropositive subjects (based on central lab test) with TEAEs and severity of TEAEs
- Incidence and severity of symptomatic SARS-CoV-2 infection in seronegative and seropositive subjects (based on central lab test) in both the EAP and follow-up periods

Cohort A and Cohort A1 Pharmacokinetic and Immunogenicity Endpoints

- Concentrations of REGN10933 and REGN10987 in serum over time and selected PK parameters in both seronegative and seropositive subjects (based on baseline central lab test)
- Immunogenicity as measured by ADAs and NAbs to REGN10933 and REGN10987 over time in both seronegative and seropositive subjects (based on baseline central lab test)

4.1.4. Cohort A and Cohort A1 Exploratory Endpoints

The exploratory endpoints for cohort A are:

- Proportion of baseline-seronegative subjects who have a first RT-qPCR confirmed SARS-CoV-2 infection in the follow-up period (ie, after day 29 visit)
- Proportion of baseline seronegative subjects who become seropositive (based on central lab test) up to day 57

- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP
- Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of the serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP
- Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during EAP
- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP
- Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of the serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP
- Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP
- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP
- Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of the serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP
- Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP
- Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR during the EAP
- Time-weighted average of viral load ($\log_{10}$ copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until third weekly visit after the first positive test in seropositive subjects (based on central lab test) during the EAP
- Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the second weekly visit after the first positive test in seropositive subjects (based on central lab test) during the EAP
- Area under the curve (AUC) in viral load ($\log_{10}$ copies/mL) in NP swab samples from the first positive SARS-CoV-2 RT-qPCR NP swab sample until the first confirmed

negative test, in seropositive subjects (based on central lab test) that has an onset during the EAP

- Proportion of subjects in the placebo group who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members participating in study R10933-10987-CoV-2067 and receiving REGN10933+REGN10987 or whose household member did not receive treatment with REGN10933+REGN10987
- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members participating in study R10933-10987-CoV-2067 and receiving REGN10933+REGN10987
- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members receiving an approved monoclonal antibody treatment for COVID-19
- Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members receiving an approved monoclonal antibody treatment for COVID-19 or REGN10933+REGN10987 in study R10933-10987-CoV-2067
- Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have asymptomatic infection during the EAP
- Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have symptomatic infection during the EAP
- Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have a medically attended visit

4.2. Cohort B and Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline

The endpoints are for all subjects who are seronegative at baseline (based on central lab test), unless stated otherwise.

4.2.1. Cohort B Primary Efficacy Endpoint

- Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

4.2.2. Cohort B Key Secondary Efficacy Endpoints

- Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of high viral load >4 (log_{10} copies/mL) in NP swab samples during the EAP

4.2.3. Cohort B and Cohort B1 Other Secondary Efficacy Endpoints

- Proportion of subjects who subsequently develop signs and symptoms (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Proportion of subjects who subsequently develop signs and symptoms (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of symptomatic SARS-CoV-2 infection (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of symptomatic SARS-CoV-2 infection (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Proportion of subjects with viral load >4 (log_{10} copies/mL) in NP swab samples during the EAP
- Change in viral load (log_{10} copies/mL) from baseline to day 8 visit in NP swab samples
- Change in viral load (log_{10} copies/mL) from baseline to day 15 visit in NP swab samples
- Time-weighted average change from baseline in viral load (log_{10} copies/mL) in NP swab samples until the day 22 visit
- Area under the curve (AUC) in viral load (log_{10} copies/mL) in NP swab samples from baseline to the first confirmed negative test
- Maximum SARS-CoV-2 RT-qPCR viral load (log_{10} copies/mL) in NP swab samples during the EAP
- Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP
- Proportion of subjects with at least one COVID-19 related hospitalization or emergency room visit associated with a positive RT-qPCR at baseline or during the EAP, or all-cause death

Additional Cohort B1 Secondary Efficacy Endpoints

- Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
- Number of weeks with high viral load >4 (log_{10} copies/mL) in NP swab samples during the EAP

Cohort B and Cohort B1 Safety Endpoints

- Proportion of subjects with TEAEs and severity of TEAEs
- Incidence and severity of symptomatic SARS-CoV-2 infection in both the EAP and follow-up periods

Cohort B and Cohort B1 Pharmacokinetic and Immunogenicity Endpoints

- Concentrations of REGN10933 and REGN10987 in serum over time and selected PK parameters in both seronegative and seropositive subjects (based on baseline central lab test)
- Immunogenicity as measured by ADAs and NAbs to REGN10933 and REGN10987 over time in both seronegative and seropositive subjects (based on baseline central lab test)

4.2.4. Cohort B and Cohort B1 Exploratory Endpoints

- Proportion of subjects who subsequently have symptomatic (strict-term) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to their baseline serology test status (ie, seropositive or other, based on central lab test)
- Proportion of subjects who subsequently have symptomatic (broad-term) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to their baseline serology test status (ie, seropositive or other, based on central lab test)
- Proportion of subjects who subsequently have symptomatic (CDC definition) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Number of weeks of symptomatic SARS-CoV-2 infection (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Number of weeks of symptomatic SARS-CoV-2 infection (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Time-weighted average change and percent change from baseline viral load (log_{10} copies/mL) by SARS-CoV-2 RT-qPCR in NP swab samples until the day 22 visit

according to baseline serology test status (ie, seropositive or other, based on central lab test)

- Area under the curve (AUC) in viral load (log_{10} copies/mL) in NP swab samples from baseline to the first confirmed negative test according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Maximum SARS-CoV-2 RT-qPCR (log_{10} viral copies/mL) in NP swab samples during the EAP according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (ie, seropositive or other, based on central lab test)
- Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have asymptomatic infection during EAP
- Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have symptomatic infection during EAP
- Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have a medically attended visit related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP

5. STUDY VARIABLES

This section provides variables to be measured in the study. For description and rationale of corresponding study procedures, refer to Section 9.2.

5.1. Demographic and Baseline Characteristics

The variables for baseline characteristics include standard demography (eg, age, race, weight, height, body mass index [BMI], risk factors for SARS-CoV-2 infection, etc), medical history, medication history, and test results for local diagnostic assay for SARS-CoV-2 from appropriate samples (details in Section 9.2.1.2), central lab SARS-CoV-2 RT-qPCR and central lab serology (anti-SARS-CoV-2 antibodies) test results for each subject.

5.2. Efficacy Variables

The efficacy variables include measurements or test results for individual subjects of the following:

- A positive SARS-CoV-2 infection (ie, a positive RT-qPCR) will be defined based on any available RT-qPCR result (either NP, nasal or saliva) which is reported as "detected". A negative infection (ie, a negative RT-qPCR) will be defined based on all available RT-qPCR results (either NP, nasal or saliva) which are reported as "not detected"
- Viral load ($\log_{10}$ copies/mL) from RT-qPCR test
- Asymptomatic SARS-CoV-2 infection: positive RT-qPCR result of NP swab sample without any of the strict-term or broad-term SARS-CoV-2 infection signs and symptoms (specified in Section 9.2.2.2) within the EAP
- Symptomatic infection based on strict-term SARS-CoV-2 infection signs and symptoms (for secondary endpoint): Positive strict-term symptomatic infection defined as SARS-CoV-2 infection signs and symptoms (specified in Section 9.2.2.2) and a positive RT-qPCR that occurs within the EAP
- Symptomatic infection based on broad-term SARS-CoV-2 infection signs and symptoms (for secondary endpoints): Positive broad-term symptomatic infection defined as SARS-CoV-2 infection signs and symptoms (specified in Section 9.2.2.2) and a positive RT-qPCR that occurs within the EAP
- Symptomatic infection based on CDC definition SARS-CoV-2 infection signs and symptoms (for secondary endpoints): Positive broad-term symptomatic infection defined as SARS-CoV-2 infection signs and symptoms (specified in Section 9.2.2.2) and a positive RT-qPCR that occurs within the EAP
- Medically attended visits to ED or UCC due to SARS-CoV-2 infection: number of visits that occur after a positive RT-PCR result within the EAP
- Hospitalization due to SARS-CoV-2 infection (hospitalization status and days in hospital) within the EAP

- Days absent from daily responsibilities (eg, days missed from work, school, childcare, or eldercare) due to SARS-CoV-2 infection within the EAP
- Occurrence of laboratory-confirmed SARS-CoV-2 infection during follow-up period collected from spontaneously reported AEs

Detailed descriptions for assessing COVID-19 signs and symptoms and their temporal relationship with lab confirmed SARS-CoV-2 infection is provided in Section 9.2.2.2.

5.3. Safety Variables

Safety variables include recording, measurements, or laboratory test results for individual subjects of the following: TEAEs; vital signs including heart rate, blood pressure, respiration rate, and body temperature, physical examination findings; results of laboratory tests including hematology, blood chemistry, and urinalysis (only for adult/adolescent subjects). In addition, subjects with a positive RT-PCR result and a medically attended visit (ED, UCC, hospitalization) will be assessed for occurrence (worst or most abnormal finding) of abnormal vital signs, respiratory failure, evidence of shock, multiorgan dysfunction and admission to ICU; Section 9.2.3).

5.4. Pharmacokinetic Variables

The pharmacokinetic variables are the concentrations of REGN10933 and REGN10987 in serum at each time point and select PK parameters. The sampling time points for dense and sparse collection schedules are specified in Table 4.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, and time-point/visit. Samples in this study will be collected at the clinic visits specified in Table 4 and Table 6.

6. STUDY DESIGN

6.1. Study Description and Duration

This is a phase 3 randomized, double-blind, placebo-controlled study in adults, adolescents, and children with household contact exposure to individuals with SARS-CoV-2 infection. This study is designed to assess the efficacy of the administration of REGN10933+REGN10987 to reduce the incidence of SARS-CoV-2 infection and prevent the development of disease (symptomatic SARS-CoV-2 infection) after household exposure to individuals with SARS-CoV-2 infection. Safety, tolerability, PK, and immunogenicity of REGN10933+REGN10987 will also be evaluated.

Eligible subjects are those who are asymptomatic and household contacts with close exposure with the first household member with known SARS-CoV-2 infection (index case) but may be either positive or negative for SARS-CoV-2 during screening, as assessed by central laboratory RT-qPCR performed at baseline. The index case will have a diagnosis of SARS-CoV-2 infection using a diagnostic test, eg, RT-PCR, antigen test, or other test format (approved or with EUA issued by the US FDA or by equivalent local health authority). Randomization will be performed by individual study subjects, not by households.

Approximately 3500 adult and adolescent subjects and approximately 250 pediatric subjects <12 years old will be enrolled. Randomization will be performed by site and stratified for assignment of treatment group by test result of a local diagnostic assay for SARS-CoV-2 from appropriate samples and age group (<12 years, ≥12 years to <18 years, ≥18 to <50 years, or ≥50 years) (Section 8.4). For pediatric subjects (<12 years), the weight group (≥20 kg, ≥10 kg to <20 kg, and <10 kg) will be used as an additional stratification factor. Cohort allocation will be based on central lab baseline SARS-CoV-2 RT-qPCR for data analysis: cohort A or cohort A1 (negative) and cohort B or cohort B1 (positive) (defined in Section 6.1.6). For adult and adolescent subjects, approximately 3150 subjects are planned to be enrolled in cohort A and 350 subjects in cohort B. At least 1248 cohort A subjects are expected to be seronegative and available for primary and secondary endpoint analysis (Section 11.2.1), excluding those cohort A subjects that were included in the administrative assessment. The subjects that are included the planned analyses are described in Section 11.4.9. For pediatric subjects (<12 years), approximately 225 subjects are planned to be enrolled in cohort A1 and 25 subjects in cohort B1. Statistical analyses will be conducted separately in each cohort. For the purpose of the study analysis, cohorts A, A1, B, and B1 are independent.

Subjects will be randomized in a 1:1 allocation ratio to 1 of 2 treatment groups (placebo or REGN10933+REGN10987) (Section 8.1).

Adult subjects were enrolled into the first 2 subgroups and then adolescents were added to subgroup 3, as subgroups 1 and 2 had completed enrollment at the time the protocol was amended to add adolescents. Subjects are assigned a subject number by IWRS (irrespective of allocation to cohort A or cohort B) (Table 4):

1. Sentinel group (subset 1; first 30 adult subjects; completed) had samples collected in the EAP and Follow-Up periods for clinical laboratory tests (hematology, blood chemistry, urinalysis), drug concentration measurement (dense, PK), and immunogenicity analysis (ADA).
2. Safety group (subset 2; 31st to 400th adult subject; completed) had samples collected in the EAP and Follow-Up periods for clinical laboratory tests (hematology, blood chemistry, urinalysis), drug concentration measurement (sparse, PK), and ADA.
3. All other subjects (subset 3; 401st to last subject) will have samples collected at baseline and end of EAP for clinical laboratory tests (hematology, blood chemistry, urinalysis) and ADA.

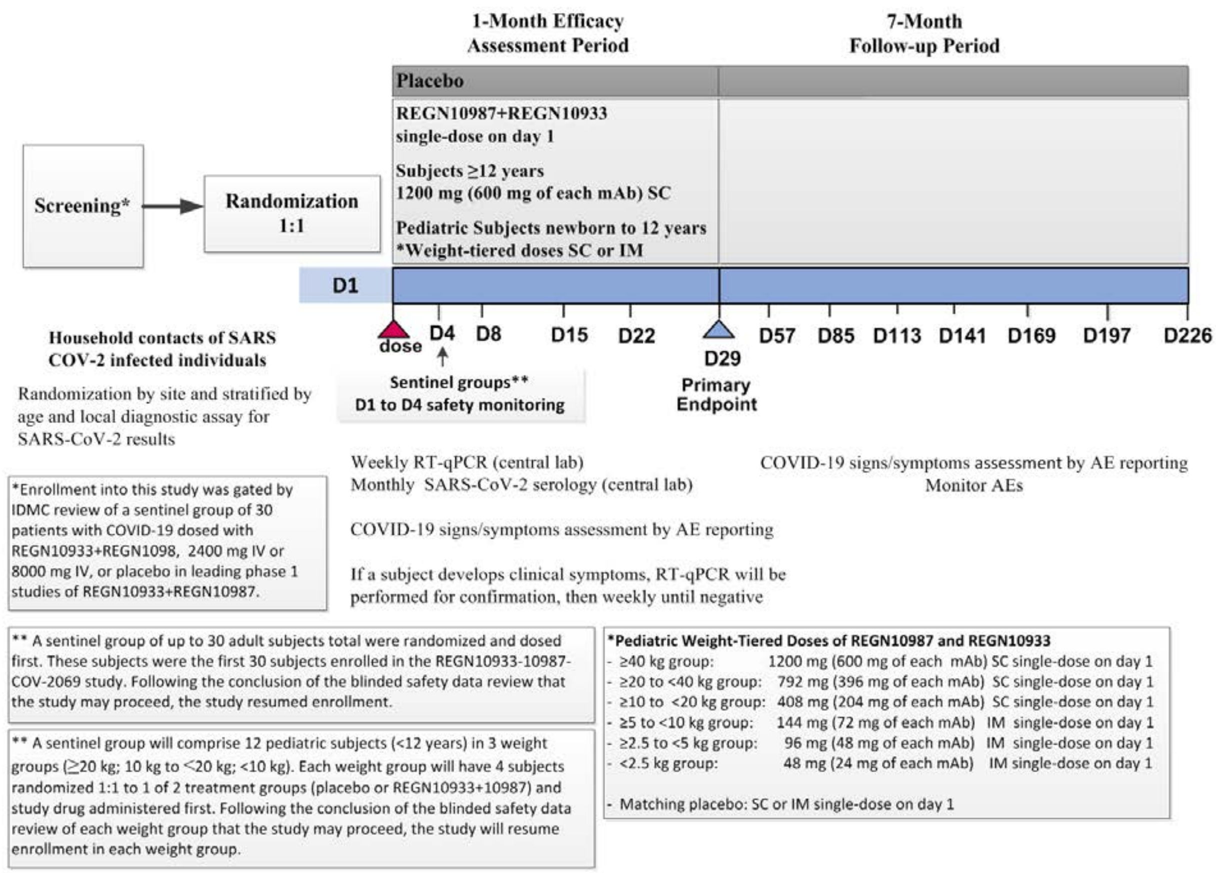
Pediatric subjects (<12 years) will be enrolled into 2 subgroups by subject number assigned by IWRS (irrespective of allocation to cohort A1 or cohort B1) (Table 6).

1. Pediatric subject sentinel group (subset 4; first 12 subjects (6 active, 6 placebo); 4 per weight group (≥20 kg, ≥10 kg to <20 kg, and <10 kg) completed) will have samples collected (Schedule A) in the EAP and Follow-Up periods for clinical laboratory tests (hematology, blood chemistry), drug concentration measurement, and ADA.
2. All pediatric subjects (subset 4 and subset 5) will have samples collected (Schedules A, B, C, and D) in the EAP and Follow-Up periods for clinical laboratory tests (hematology, blood chemistry), drug concentration measurement, and ADA.

For each subject, the study comprises 3 periods: a 1-day screening/baseline period, a 1-month EAP, and a 7-month follow-up period.

The study flow diagram is provided in Figure 1.

Figure 1: Study Flow Diagram



6.1.1. Sentinel Subjects and Staggered Enrollment/Dosing:

Enrollment into this study was gated by IDMC review of a sentinel group of 30 adult patients with COVID-19 dosed with REGN10933+REGN10987 2400 mg IV, REGN10933+REGN10987 8000 mg IV or placebo in leading phase 1 studies of REGN10933+REGN10987 (Section 3.2.4).

Enrollment in this study was carried out in 2 phases:

1. Sentinel group comprised ~30 adult subjects (by subject number assigned by IWRS; irrespective of allocation to cohort A or cohort B): Subjects were monitored for safety on-site for a minimum of 4 hours after administration of the first dose of study drug and then daily via visits to the study site or phone calls for the first 4 days (96 hours). Because REGN10933+REGN10987 will already have cleared an adult safety sentinel cohort at higher doses administered IV in previous studies (Section 3.2.4), the sentinel group in this study focused on safety evaluation for injection site reactions and hypersensitivity reactions and data were reviewed before progressing with enrollment of additional study subjects. The blinded safety data review was be led by a designated member of the Regeneron

clinical team (generally either the medical monitor or the clinical trial manager) and at a minimum the data review team included the Regeneron Medical Monitor, Study Biostatistician, Global Safety Lead or designee, and the Senior Vice President of Early Clinical Development & Experimental Sciences.

2. Following a conclusion of the blinded safety data review that the study could proceed, the study resumed enrollment.

In case of any safety concerns, the IDMC/DMSB may be consulted and requested to provide recommendations.

6.1.2. Pediatric Subjects (<12 years)

Approximately 250 pediatric subjects (<12 years) across all weight-tiered dose ranges will be enrolled. However, since the enrollment of pediatric subjects (<12 years) will end once enrollment of adult and adolescent subjects is complete, the number of pediatric subjects may be adjusted.

Enrollment of pediatric subjects in this study will be carried out in 2 steps, one for safety and another for confirmation of drug exposure for each weight group.

Pediatric Subjects Safety Sentinel Group

1. Sentinel group (subset 4) will comprise 12 pediatric subjects (by subject number assigned by IWRS; irrespective of allocation to cohort A1 or cohort B1) in 3 weight groups (≥20 kg; 10 kg to <20 kg; <10 kg). Each weight group will have 4 subjects randomized 1:1 to 1 of 2 treatment groups (placebo or REGN10933+REGN10987) and study drug administered first. After all 4 subjects in a weight group complete the sentinel review, enrollment of additional subjects in that weight group will proceed. Pediatric subjects (<12 years) will be monitored for safety on-site for a minimum of 2 hours after administration of the first dose of study drug and then daily via visits to the study site or phone calls for the first 4 days (96 hours). Because REGN10933+REGN10987 will already have cleared an adult safety sentinel cohort at higher doses administered IV in previous studies (Section 3.2.4), and the adult safety sentinel as well as the first 20 adolescent subjects (≥12 to <18 years) in this study, the pediatric (<12 years) sentinel group in this study is focused on safety evaluation for injection site reactions and hypersensitivity reactions and data will be reviewed before progressing with enrollment of additional pediatric subjects. The blinded safety data review will be led by a designated member of the Regeneron clinical team (generally either the medical monitor or the clinical trial manager) and at a minimum the data review team will include the Regeneron Medical Monitor, Study Biostatistician, Global Safety Lead or designee, and the Senior Vice President of Early Clinical Development & Experimental Sciences.
2. Following a conclusion of the blinded safety data review that the study may proceed for a weight group, the enrollment of pediatric subjects in that weight group will resume; however, close monitoring by the Safety Review Committee will continue on a periodic cumulative aggregate basis, including stratification to facilitate early and periodic review of data for adolescent subjects (≥12 years to <18 years) and pediatric subjects (<12 years) in each of the weight groups.

Confirmation of Drug Exposure for Pediatric Subjects Weight Groups

1. All pediatric subjects (subset 4 and subset 5) will have samples collected (Schedules A, B, C, and D) in the EAP and Follow-Up periods for drug concentration measurement as well as ADA assessment and clinical laboratory tests (hematology, blood chemistry). The drug concentration data from approximately the first 20 subjects per weight group (<10 kg, 10 to 20 kg, ≥20 kg) will be evaluated to confirm that the REGN10933 and REGN10987 dose for the weight group is providing the expected exposure.
2. Based on simulations using a population PK model using data from adult patients with COVID-19, the proposed doses for the pediatric subjects (Table 2) is expected to match the exposure in adult subjects at SC dose of 1200 mg (600 mg per mAb) in this study. Once the exposure for a dose is confirmed in a weight group, enrollment beyond 25 subjects for this weight group can continue. Based on the results of the drug concentration analyses from up to 20 pediatric subjects receiving active drug in the weight groups, the dose for participating pediatric subjects may be adjusted in 1 or more of the weight group(s) to ensure drug exposure comparable to adult subjects in this study. If the dose for a particular weight group needs to be adjusted, the new dose for that weight group will used for approximately a subsequent 20 subjects for that weight group. These subjects who received the new dose will have drug concentrations analyzed to confirm that it is providing the expected exposure. When the new dose is started, the subjects will resume dosing according to the next sample collection schedule since the last subject received study drug.

6.1.3. Screening/Baseline

After subjects provide informed consent, they will be assessed for study eligibility. The screening visit and randomization visit should occur on the same day. If needed, a remote visit may occur to sign the ICF and collect medical history and concomitant medication use, on the day prior to, but within 24 hours of study drug administration, so that the in person screening and randomization visit may be abbreviated, due to COVID-19 considerations. Study drug administration must occur within 96 hours of the sample collection of the index cases' positive SARS-CoV-2 diagnostic test sample. Subjects will be provided with contact information for the clinical study site and will be given written and verbal instructions to call site personnel with any changes in their health status.

On day 1, prior to randomization, a local diagnostic assay for SARS-CoV-2 (SARS-CoV-2 antigen or RT-PCR) from appropriate samples will be performed (details in Section 9.2.1.2). The result of this assay will be used as a stratification factor for randomization to treatment groups (placebo or REGN10933+REGN10987) (Section 8.4). The requirement for a local diagnostic assay for SARS-CoV-2 is waived when the results are not expected to be available in a timely manner for randomization. Nasopharyngeal swab sample (swabbing through both nostrils) for central lab testing of SARS-CoV-2 RT-qPCR and blood sample for central lab serology will be collected and sent to central lab. After completing baseline assessments and sample collection, all subjects will receive a single-dose of study drug (see details of study drug administration in Section 8.1). The central lab results of baseline SARS-CoV-2 RT-qPCR will be used to allocate subjects into cohort A (negative result) or cohort B (positive result).

Subjects will be monitored for vital signs and TEAEs after study drug administration as follows:

- **Adult subjects in the sentinel group (subset 1; completed)** were monitored in the clinic for at least 4 hours after study drug administration on day 1 and then daily by phone call or site visit until day 4 (96 hours).

- **Adult subjects in the safety group (subset 2; completed)** were monitored in the clinic every hour for 2 hours after study drug administration and by a phone call on day 4.
- **All other adult and adolescent subjects (subset 3)** will be monitored in the clinic for 1 hour after study drug administration.
- **Pediatric subjects (<12 years) in the sentinel group (subset 4)** will be monitored in the clinic for at least 2 hours after study drug administration on day 1 and then daily by phone call or site visit until day 4 (approximately 96 hours).
- **All other pediatric subjects (<12 years) (subset 5)** will be monitored in the clinic for 1 hour after study drug administration.

All subjects will be advised to call the site if signs/symptoms of hypersensitivity occur. During post-dose monitoring, Grade 3 or greater injection site reactions and hypersensitivity reactions that occur after study drug administration will be captured as an AESI to allow for expedited reporting to the sponsor (see AE grading system in Section 10.2.4 and list of AESIs in Section 10.1.3).

6.1.4. Efficacy Assessment Period

Efficacy, safety, sample collections, and other study assessments will be performed at specified time points throughout the EAP according to the Schedule of Events specified in Section 9.1. On day 1/baseline with study drug administration, sample collection must occur prior to study drug administration.

If subjects are able to travel and can do so while maintaining social distancing guidelines, subsequent site visits will be conducted; alternatively, telemedicine visits, phone calls, mobile units or home health nurses may be utilized. Throughout the study, biological samples will be obtained by adequately trained and delegated study personnel at study locations where appropriate personal protective equipment (PPE) are available to be used.

At each weekly visit, assessments and procedures will be performed (Table 3 and Table 4). Subjects will be instructed to contact the study site staff for any new or changing symptoms or signs possibly related to COVID-19, including fever. The investigator should recommend that subjects (themselves or by their parent/guardian) measure their temperature daily during EAP, approximately at the same time, and also every time when the subject feels feverish, chills, or sick (Section 10.1.1). Adult subjects may receive automated reminders (eg, text messages to mobile phones; implemented as soon as technologically feasible and when subjects confirm to opt in) in between the weekly visits to prompt them to contact the study site staff as needed. The NP swab sample will be collected for SARS-CoV-2 RT-qPCR to be tested at the central lab. The investigator or designee will contact each subject weekly (site visit or telemedicine) to assess the subjects general health, and to document AEs in general and any signs and symptoms associated with SARS-CoV-2 infection since the last contact (see details of the procedure in Section 9.2.2.2).

Any subject who develops fever, an acute respiratory illness, symptoms related to multisystem inflammatory syndrome in children ([MIS-C] [pediatric subjects <18 years only]), or other symptoms that they may feel could be related to COVID-19 should alert the study staff immediately. If the subject experiences a true medical emergency, they should visit their local hospital ED or call the local emergency telephone number (eg, 911 in North America) and contact the clinical site personnel later. Subjects' symptoms must be evaluated by the investigator or designee, which can occur through site visit, mobile unit, home visit, telemedicine, etc. If investigator or designee suspects SARS-CoV-2 infection, a NP swab sample should be collected and sent for central lab testing. The subject may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1).

Subjects with laboratory confirmed SARS-CoV-2 infection should be informed as soon as possible and should undergo medical isolation to prevent contact with others to reduce the risk of further transmission. Since these subjects will likely be isolated, the study visits, assessments and sample collections may occur through a variety of methods. For subjects who have a confirmed SARS-CoV-2 infection, the investigator will assess AEs weekly or more frequently than weekly, depending on the clinical status of the subject, as assessed by the investigator or designee (these more frequent AE assessments will be reported as unscheduled visits). The investigator will also collect information for any SARS-CoV-2 infection-related medically attended visits to the ED, UCC, or hospitalization starting from the timepoint of SARS-CoV-2 RT-qPCR positive result (see detail in Section 9.2.2.3).

For subjects who are positive for SARS-CoV-2 at any time during the EAP, including those positive at baseline, subsequent assessments/sample collections in the EAP should follow that specified in Table 3 until 2 consecutive confirmed negative SARS-CoV-2 RT-qPCR test results are achieved ≥24 hours apart. A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

Subjects presenting with acute illness should be medically managed according to local standard of care as per the discretion of the treating physician.

If a subject is hospitalized for suspected COVID-19, every effort should be made by the site personnel to collect, as soon as possible, a NP swab sample for central lab SARS-CoV-2 RT-qPCR testing. In subjects where it is not possible to have samples collected for assessment in the central laboratory, study site personnel will attempt to obtain and record information about all SARS-CoV-2 assays conducted in other medical facilities, including result(s), name of the assay(s) and whether the laboratory(ies) conducting the assays is a CLIA (Clinical Laboratory Improvement Amendments) certified (or equivalent) laboratory. The laboratory report for a positive SARS-CoV-2 test result, including the name of the test as well as information about laboratory certification, should be collected and stored as source documentation at the site. The positive SARS-CoV-2 assay result will be recorded in concomitant procedures related to the COVID-19 AE. Details on any symptoms and medically attended visits will also be collected. After discharge, as described above, all subjects with a positive SARS-CoV-2 RT-PCR will continue to follow the weekly planned study visits until 2 confirmed negative SARS-CoV-2 RT-qPCR test results are achieved at least 24 hours apart.

6.1.5. Follow-up Period

Subjects who remain SARS-CoV-2 RT-qPCR negative throughout the EAP will complete the end of the EAP and enter the Follow-up Period to be followed for 7 months (Table 3, Table 4).

Subjects who become SARS-CoV-2 RT-qPCR positive during the EAP will continue to have weekly NP swab samples for SARS-CoV-2 RT-qPCR tests until 2 confirmed negative

SARS-CoV-2 RT-qPCR test results are achieved at least 24 hours apart, even after they complete the EAP and enter the study Follow-up Period to be followed for 7 months. In such situations, these visits for sample collection in the Follow-up Period should be characterized as unscheduled visits. A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

At each scheduled visit, the investigator or designee will contact each subject (site visit or telemedicine) to assess and document the subject's general health, AEs in general and signs and symptoms associated with SARS-CoV-2 infection, including fever, since the last contact, as described for the EAP (Section 6.1.4). For subjects who have a confirmed SARS-CoV-2 infection, the investigator will assess AEs weekly or more frequently than weekly, depending on the clinical status of the subject, as assessed by the investigator or designee (these more frequent AE assessments will be reported as unscheduled visits). The investigator will also collect information for any SARS-CoV-2 infection-related medically attended visits to the ED, UCC, or hospitalization starting from the timepoint of SARS-CoV-2 RT-qPCR positive result (see details in Section 9.2.2.3).

Any subject who, between the study visits, develops fever, an acute respiratory illness, symptoms related to MIS-C (pediatric subjects <18 years only), or other symptoms that they may feel could be related to COVID-19 should alert the study staff immediately. If the subject experiences a true medical emergency, they should visit their local hospital ED or call the local emergency telephone number (eg, 911 in North America) and contact the clinical site personnel later. The subjects' symptoms must be evaluated by the investigator or designee, which can occur through site visit, mobile unit, home visit, telemedicine, etc. If the investigator or designee deems the subject's signs/symptoms require the collection of biological samples for central lab testing to assess or confirm SARS-CoV-2 infection, the subject will be advised to provide NP sample. The subject may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1). If a subject is hospitalized for suspected COVID-19, every effort should be made by the site personnel to collect, as soon as possible, a NP swab sample for central lab SARS-CoV-2 RT-qPCR testing. In subjects where it is not possible to have samples collected for assessment in the central laboratory, study site personnel will attempt to obtain and record information about all SARSCoV-2 assays conducted in other medical facilities, including result(s), name of the assay(s) and whether the laboratory(ies) conducting the assays is a CLIA certified (or equivalent) laboratory. The laboratory report for a positive SARSCoV-2 test result, including the name of the test as well as information about laboratory certification, should be collected and stored as source documentation at the site. The positive SARS CoV-2 assay result will be recorded as concomitant procedures related to the COVID-19 AE. Details on any symptoms and medically attended visits will also be collected.

6.1.6. Description of Study Cohorts

The study has 4 independent cohorts, cohort A and cohort B for adult and adolescent subjects and cohort A1 and cohort B1 for pediatric subjects <12 years.

All subjects enrolled in the study will be household contacts of the first household members with a diagnosis of SARS-CoV-2 (index case) and asymptomatic at the time of screening. The subjects'

SARS-CoV-2 infection status, positive or negative by SARS-CoV-2 RT-qPCR (central lab) at baseline, determines the study procedures they follow (SOE) and the analysis of endpoints.

- **Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline:** Approximately 3150 adult and adolescent subjects with a negative SARS-CoV-2 RT-qPCR result who are asymptomatic at baseline. Cohort A will evaluate the efficacy of a single dose of REGN10933+REGN10987 as prophylaxis to prevent SARS-CoV-2 symptomatic infection.
- **Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline:** Approximately 350 adult and adolescent subjects with a positive SARS-CoV-2 RT-qPCR result who are asymptomatic at baseline. Cohort B will evaluate the effect of a single-dose of REGN10933+REGN10987 as preemptive therapy to prevent or modify symptomatic disease.
- **Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline:** Approximately 225 pediatric subjects (<12 years) with a negative SARS-CoV-2 RT-qPCR result who are asymptomatic at baseline.
- **Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline:** Approximately 25 pediatric subjects (<12 years) with a positive SARS-CoV-2 RT-qPCR result who are asymptomatic at baseline.

Study objectives and endpoints are specified for each cohort (Section 2 and Section 4).

The statistical analysis sets for the cohorts are defined in Section 11.3.1.

6.1.7. Study Stopping Rules

6.1.7.1. Study Stopping Criteria

The IDMC, which may also be referred to Data and Safety Monitoring Board (DSMB), will monitor unblinded data on a regular basis to assess the risk/benefit profile of REGN10987+REGN10933. If at any time the IDMC has significant concerns regarding a meaningful imbalance in TEAEs or treatment-emergent SAEs, including in relation to safety data by pediatric groups, the IDMC may make a recommendation to the Sponsor to halt the study or make recommendations for other changes in the study conduct. This will prompt a review by the Sponsor who will decide to implement, modify, or reject the recommendation. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

Pre-specified stopping rules for early termination (ET) of the study for efficacy will be documented in the Statistical Analysis Plan (SAP) and IDMC Charter.

6.1.8. End of Study Definition

The end of study is defined as the date the last subject completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study subject can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

There is no interim analysis planned after the administrative assessment.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee/Data and Safety Monitoring Board

The terms IDMC and DSMB employed during the conduct of this study refers to the safety committee that will perform safety monitoring for this study and the terms are interchangeable in this protocol.

The IDMC/DSMB, will be utilized to evaluate the safety of REGN10933+REGN10987 on a regular basis. The IDMC/DSMB is important for this prophylaxis study, given the limited amount of safety data currently available, and because the study will enroll a large number of adults. The IDMC/DSMB may also be asked to perform a formal interim evaluation of efficacy (Section 11.5) and/or sample size re-estimation to be conducted when 25% of the originally planned number of subject complete the EAP (Section 11.2.1). The details of such evaluation will be described in the IDMC/DSMB Charter.

6.3.2. Safety Review Committee for REGN 2069/ CoVPN 3502

The Safety Review Committee (SRC) for REGN 2069/CoVPN 3502 will include Regeneron members (Medical/Study Director(s), Global Patient Safety, and Biostatistics and Data Management), National Institute of Allergy and Infectious Diseases (NIAID) members (Medical Officers), and CoVPN members (Protocol Chairs, and the CoVPN Physician. The CoVPN is supported by NIAID. The SRC for 2069/CoVPN 3502 will be utilized to evaluate the safety of REGN10933+REGN10987 on a regular basis. Safety monitoring will be performed for blinded data on an ongoing basis (eg, individual review of SAEs and AESIs) and on a periodic cumulative aggregate basis, including stratification to facilitate early and periodic review of data for adolescent subjects (≥12 years to <18 years), pediatric subjects (<12 years), and pregnant and breastfeeding subjects. The details of the safety monitoring will be described in the SRC for 2069/CoVPN 3502 safety monitoring collaborative plan.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

7.1. Number of Subjects Planned

Cohort A: SARS-CoV-2 RT-qPCR Negative at Baseline- Approximately 3150 adult and adolescent subjects will be enrolled. Cohort A is expected to include the majority of study subjects.

Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline- Approximately 350 adult and adolescent subjects will be enrolled.

Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline- Approximately 225 pediatric subjects (<12 years) will be enrolled.

Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline- Approximately 25 pediatric subjects (<12 years) will be enrolled.

7.2. Study Population

Eligible subjects for this study consist of asymptomatic, healthy adults and children who are household contacts to the first known household member with a diagnosis of SARS-CoV-2 infection (index case).

7.2.1. Inclusion Criteria

A subject must meet the following criteria to be eligible for inclusion in the study:

1. Adult subjects 18 years of age (irrespective of weight) and above at the signing of informed consent or adolescent subjects ≥12 to <18 years of age, or pediatric subjects <12 years of age at the signing of the assent (parent/guardian sign the informed consent) (see Section 13.2)
2. Asymptomatic household contact with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case). To be included in the study, subjects must be randomized within 96 hours of collection of the index cases' positive SARS-COV-2 diagnostic test sample
3. Subject anticipates living in the same household with the index case until study day 29
4. Is judged by the investigator to be in good health based on medical history and physical examination at screening/baseline, including subjects who are healthy or have a chronic, stable medical condition
5. Willing and able to comply with study visits and study-related procedures/assessments.
6. Provide informed consent signed by study subject or legally acceptable representative.

7.2.2. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Subject-reported history of prior positive SARS-CoV-2 RT-PCR test or positive SARS-CoV-2 serology test at any time before the screening
2. Subject has lived with individuals who have had previous SARS-CoV-2 infection or currently lives with individuals who have SARS-CoV-2 infection, with the exception of the index case(s), the first individual(s) known to be infected in the household
3. Active respiratory or non-respiratory symptoms consistent with COVID-19
4. History of respiratory illness with sign/symptoms of SARS-CoV-2 infection, in the opinion of the investigator, within the prior 6 months to screening
5. Nursing home resident
6. Any physical examination findings, and/or history of any illness, concomitant medications or recent live vaccines that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the subject by their participation in the study

7. Current hospitalization or was hospitalized (ie, >24 hours) for any reason within 30 days of the screening visit
8. Has a history of significant multiple and/or severe allergies (eg, latex gloves), or has had an anaphylactic reaction to prescription or non-prescription drugs or food. This is to avoid possible confounding of the safety analysis and not due to any presumed increased risk of these individuals to a reaction to the investigational product
9. Treatment with another investigational agent in the last 30 days or within 5 half-lives of the investigational drug, whichever is longer, prior to the screening visit
10. Received an investigational or approved SARS-CoV-2 vaccine
11. Received investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (eg, convalescent plasma or sera, monoclonal antibodies, hyperimmune globulin)
12. Use of hydroxychloroquine/chloroquine for prophylaxis/treatment of SARS-CoV-2 or anti-SARS-viral agents, eg, remdesivir, within 60 days of screening

    NOTE: hydroxychloroquine/chloroquine for other uses, eg, for use in autoimmune diseases is allowed
13. Member of the clinical site study team and/or immediate family
14. Exclusion criterion #14 excluding sexually active men who are unwilling to use the following forms of medically acceptable birth control during the study drug follow-up period and for 8 months after single dose of study drug was removed since enrollment was expanded to include all women in protocol amendment 4.
15. Exclusion criterion #15 excluding pregnant or breastfeeding women was removed since enrollment was expanded to all women in protocol amendment 4.
16. Exclusion criterion #16 excluding women of childbearing potential (WOCBP)* and girls at or beyond menarche (≥12 to <18 years of age) who were unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 8 months after the last dose was removed since enrollment was expanded to all women in protocol amendment 4.

    *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

7.3. Premature Withdrawal from the Study

A subject or pediatric subject's parent/guardian has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or Sponsor have the right to withdraw a subject from the study if it is no longer in the interest of the subject to continue in the study, or if the subject's continuation in the study places the scientific outcome of the study at risk (eg, if a subject does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

Subjects who are withdrawn prematurely from the study will be asked to complete the ET visit, as described in Section 9.1.5.

7.4. Replacement of Subjects

Subjects prematurely discontinued from study will not be replaced.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

The following drug product will be provided. Instructions on dose preparation are provided in the pharmacy manual.

REGN10933 and REGN10987, to be co-administered:

- REGN10933: Supplied as a 120 mg/mL solution for SC or IM injection
- REGN10987: Supplied as a 120 mg/mL solution for SC or IM injection

Matching placebo:

- Supplied as matching solution for SC or IM injection.

All adult or adolescent subjects will receive 4 SC injections of study drug on day 1, each injection containing 2.5 mL of active study drug or placebo. The REGN10987 and REGN10933 dose is 1200 mg (600 mg of each mAb) SC single dose on day 1.

Pediatric subjects (<12 years of age) will receive between 1 to 4 SC or IM injections of study drug, active or placebo, depending on the weight-tiered dose group on day 1 (Table 2). Subjects <5 kg should not receive an injection with more than 1 mL, subjects between 5 and 10 kg should not receive an injection with more than 1.25 mL. Subjects <10 kg may receive IM injection(s)at the discretion of the investigator, as children less than 10 kg have smaller amounts of subcutaneous tissue and IM injection may be better tolerated than SC. In addition, in children <10 kg, the combined volume containing both mAbs may be administered in a single syringe. The total volume of study drug per syringe and the number of injections will be recorded in the CRF. For subjects who weigh ≥10 kg, study drug may be administered SC using an infusion pump, containing the combined volume containing both mAbs, which may improve tolerability of administration as only 1 injection may be required.

Table 2: Weight-Tiered Dose Groups for Pediatric Subjects <12 Years of Age

Weight-Tiered Dose Group	Total Dose (mg)	Route of Administration	Total Number of Injections	Total Volume (mL) of Injection
≥40 kg	1200 (600 per mAb)	SC[1]	4	10 (5 per mAb)
≥20 to <40 kg	792 (396 per mAb)	SC[1]	4	6.6 (3.3 per mAb)
≥10 to <20 kg	408 (204 per mAb)	SC[1]	2 or 4	3.4[2] (1.7 per mAb)
≥5 to <10 kg[3]	144 (72 per mAb)	IM	1 or 2	1.2[4] (0.6 per mAb)
≥2.5 to <5 kg[3]	96 (48 per mAb)	IM	1	0.8 (0.4 per mAb)
<2.5 kg[3]	48 (24 per mAb)	IM	1	0.4 (0.2 per mAb)

1. Investigators have the option to use an infusion pump for SC administration of study drug containing the combined volume with both mAbs.
2. If the Investigators prefers not to exceed 1 mL per syringe, then study drug may be administered using 2 syringes for each mAb (ie, 4 injections), one with 0.8 mL and another with 0.9 mL for each mAb. If the Investigator prefers to use only 2 syringes (ie, 2 injections), the 1.7 mL administered in each syringe will contain a different mAb.
3. Investigators have the option to administer the dose in a single syringe containing the combined volume with both mAbs.
4. If the Investigator prefers not to exceed 1 mL per syringe, then study drug may be administered using 1 syringe for each mAb. If the Investigator prefers to use 1 syringe, the1.2 mL administered in 1 syringe should be combined volume of 0.6 mL of each mAb.

For study drug administration which requires multiple SC injections, it is recommended to use different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs. During the dose administration, each injection must be given in a different anatomical location (eg, 1 injection administered in the right lower quadrant of the abdomen, another in the left lower quadrant of the abdomen, etc). For pediatric subjects (<12 years) only, a numbing cream may be used at the planned site(s) of injection. Adolescent (≥12 years) and adult subjects should not use numbing cream at the sites of injection as this will interfere with the safety assessment, ie, evaluation of injection site reactions.

A pharmacist or qualified personnel at the site, not otherwise associated with the conduct of the study, will prepare the drug for SC administration or IM administration. The prepared syringe must be provided in identical form for active and placebo treatments, so that they remain indistinguishable to both study personnel and subject. Details for study drug administration are provided in the pharmacy manual.

8.2. Dose Modification and Study Treatment Discontinuation Rules

8.2.1. Dose Modification

This is a single dose study; dose modification is not allowed.

8.2.2. Study Drug Discontinuation

This is a single dose study; study drug discontinuation is not applicable.

8.3. Management of Acute Reactions

8.3.1. Acute Injection Reactions

8.3.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4.

Acute systemic reactions following injection of study drug (subcutaneous [SC]) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.3.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4.

8.4. Method of Treatment Assignment

Subjects will be randomized in a 1:1 ratio to receive REGN10987+REGN10933 or placebo according to a central randomization scheme provided by an interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be performed by individual study subjects, not by households. In addition to a randomization number, all subjects randomized will be given a household identification number in the case that multiple members of the same household are enrolled and receive study drug. This ensures that any correlation among subjects within the same household may be considered in the statistical analysis. The REGN10987 and REGN10933 dose for adult, adolescent, and pediatric subjects is described in Section 8.1.

Randomization will be performed by site and stratified as follows:

- Local diagnostic assay for SARS-CoV-2 from appropriate samples (positive, negative, or undetermined)
- Age and/or weight:
  - <12 years and <10 kg,
  - <12 years and ≥10 kg to <20 kg,
  - <12 years and ≥20 kg
  - ≥12 years and <18 years
  - ≥18 years and <50 years
  - ≥50 years

Note that the cohorts used in the analysis are defined by the baseline central lab SARS-CoV-2 RT-qPCR results, not by the local diagnostic assay.

8.5. Blinding

Study subjects, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron Medical/Study Director, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study sites will remain blinded to all subject randomization assignments.

No interim analyses were conducted (Section 11.5) and an unblinded administrative assessment of study assumptions (Section 11.2) was conducted. No study personnel involved in the day-to-day conduct of the study will have access to any subject-level unblinded data before the final database is locked for this study.

Anti-drug antibody, drug concentration results, and central lab serology results will not be communicated to the sites. The Sponsor's blinded study team will not have access to post-baseline results associated with subject identification until after the database is locked for the respective study part.

8.6. Emergency Unblinding

Unblinding of treatment assignment for a subject may be necessary due to a medical emergency or any other significant medical event and when a treatment decision is contingent on knowing the subject's treatment assignment.

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected subjects will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the subject. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.
- The investigator will notify Regeneron and/or designee as soon as possible after unblinding the subject for safety or other important medical decisions, however, unblinding performed for the purpose of COVID-19 vaccine decision making does not need to be discussed with the medical director.

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the subject's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label blinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.7.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed at the site with approval by the Sponsor or returned to the Sponsor or designee.

8.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each subject
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.7.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the Sponsor and regulatory agency inspectors.

8.8. Concomitant Medications and Procedures

Any treatment administered from the single dose of study drug to final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

As per Section 6.1.4 and Section 6.1.5, a positive SARS-CoV-2 test which is associated with a symptomatic SARS-CoV-2 infection and is conducted in a local laboratory associated with a medical facility, should be recorded as a concomitant procedure and associated with the COVID-19 AE.

8.9. Prohibited Medications

Treatment with the following concomitant medications as prophylaxis is prohibited in uninfected subjects or for treatment of asymptomatic infection during the EAP and Follow-Up Period and may result in permanent discontinuation from the study.

1. Other investigational drugs
2. Investigational SARS-CoV-2 vaccine
3. Approved or EUA approved SARS-CoV-2 vaccine (prohibited only during the EAP)
4. Investigational or approved passive antibodies for SARS-CoV-2 infection prophylaxis (eg, convalescent plasma or sera, monoclonal antibodies, hyperimmune globulin)
5. Hydroxychloroquine/chloroquine prescribed for the prophylaxis or treatment of COVID19 (*Note Hydroxychloroquine/chloroquine used for other indications eg, autoimmune therapies are permitted.)*
6. Remdesivir or anti-SARS-viral agents

8.10. Permitted Medications

Other than the prohibited medications listed in Section 8.9, treatment with concomitant medications is permitted during the study. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

Subjects with symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the study will be treated according to local standard of care as per the discretion of the investigator or treating physician. Any medication used by the study subject should be captured in the concomitant medication eCRF.

Subjects are permitted to receive an approved or EUA approved COVID-19 vaccine after they complete the EAP.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

Study assessments and procedures for adult and adolescent subjects and pediatric subjects <12 years old are presented by study period and visit in Table 3 and Table 5 for the period from screening/baseline to end of the EAP and the Follow-up Period, and in Table 4 and Table 6 for sample collection for assay of drug concentration and ADA, as well as for safety clinical labs during the entire study.

Refer to Section 6.1.4 for conducting study assessments and sample collection when a subject is positive for SARS-CoV-2 infection based on rapid RT-PCR or RT-qPCR and when a subject is hospitalized.

Table 3: Schedule of Events Cohorts A and B ([Adult / Adolescent Subjects], RT-qPCR-Negative and Positive)

Visit	Screening / Baseline[1]	Additional Safety (Sentinel Only)[2]				Efficacy Assessment Period (EAP)[3]				Follow-up Period							ET	Unscheduled Visit[4]
Visit Location Site (S), Phone (P)[5]	**S**	**S**	**S**	**P**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**		
Visit Number	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS**		
Day	1	1	2	3	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)						±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Screening/Baseline:																		
Inclusion/exclusion	X																	
Informed consent (adult subject or parent/guardian)/pediatric assent (adolescent subject)	X																	
Informed consent(adults or parent/guardian)/pediatric assent for PGx sub-study(optional)[6]	X																	
Medical history	X																	
Demographics and risk factors for SARS-CoV-2 infection	X																	
Household assessment	X[16]								X									
Appropriate sample, diagnostic assay for SARS-CoV-2 (local lab)	X[7]																	
Randomization	X																	
Treatment:																		
Study drug administration	X[8]																	
Efficacy (Virology):																		
NP swab, SARS-CoV-2 RT-qPCR (central lab)[7,17]	X[8]					X	X	X	X	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X	X
Efficacy (Subject-Reported) only for RT-qPCR positive subjects:																		
Assessment of ED, UCC, hospital visits[18]						X	X	X	X	X	X	X	X	X	X	X		
Absenteeism assessment[18]						X	X	X	X							X		
Safety:																		
Vital signs	X[2,11]	X[2]							X							X		X
Targeted PE[11]	X		X		X				X							X		X
Adverse events[15,19]	X	X[2]	X[2]	X[2]	X[2,10]	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds, Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test for WOCBP (dipstick, local lab)[12]	X															X		X
Laboratory Testing[13]:																		
Clinical Laboratory, Hematology, Blood Chemistry, Urinalysis	Refer to Table 4																	
Pharmacokinetics and Immunogencity[13]:																		
Drug concentration	Refer to Table 4																	
Anti-drug antibodies (ADA)																		
Biomarkers:																		
Serum for serology (central lab)[14]	X								X	X						X		

Research plasma	X								X[20]	X[20]						X[20]		
Research serum	X								X[20]	X[20]						X[20]		
Pharmacogenomics Sub-Study:																		
Whole Blood for RNA (Optional)[6]	X								X[20]	X[20]						X[20]		
Whole Blood for DNA (Optional)[6]	X																	
EAP, Efficacy assessment period; EOS, end of study; ED, emergency departments; ET, Early termination; UCC, urgent care centers; PE, physical exam; PGx, pharmacogenomics; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.																		

9.1.1. Schedule of Events Table 3 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes

1. The screening visit and baseline visit should both occur on the same day. If needed, a remote visit may occur to sign the ICF and collect medical history and concomitant medication use, on the day prior to, but within 24 hours of study drug administration, so that the in-person screening and randomization visit may be abbreviated, due to COVID-19 considerations. Study drug administration must occur within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.
2. The sentinel group (see Section 6.1.1) had additional safety monitoring on day 1 and through day 4.

   Vital signs: On day 1, vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) will be measured at predose, approximately every 30 minutes during the first 2 hours after dose, at hour 3, and at hour 4 before dismissal.

   Adverse Events (injection site reactions and hypersensitivity): after the administration of the first dose of study drug, subjects will be monitored on site for a minimum of 4 hours and then by daily visits to the study site or phone calls for the first 4 days (96 hours), particularly focusing on the assessment of injection site reactions and hypersensitivity after study drug administration.
3. Subjects who have a positive RT-PCR result during screening, or who have a positive RT-qPCR result any time after screening, will have the additional assessments done as indicated (**RT-qPCR positive subjects only**). A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

   For subjects who become RT-qPCR positive after screening, the visit schedule will proceed as follows: (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.
4. Unscheduled visits: If, at any time after randomization until end of study, a subject develops fever, an acute respiratory illness or other symptoms they may feel could be related to COVID-19 or is hospitalized for suspected COVID-19, the subject or parent/guardian (adolescent pediatric subject) should alert the investigator or designee immediately who will assess the subject's symptoms and condition (can be performed by phone contact, telemedicine, online meeting, home health care, etc) to decide if the subject should have an unscheduled visit for collection of NP swab sample for RT-qPCR testing. The subject or parent/guardian (adolescent pediatric subject) may also be asked to provide

blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1). The investigator or designee should query the subject about AEs in general and AEs consistent of COVID-19 and record the information on CRF (see detailed description of the procedure in Section 9.2.2.2).

(a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

5. Visit may occur by phone or electronic means
6. Separate consent (adult subject or parent/guardian of adolescent pediatric subject)/pediatric assent is required for participation in the optional genomic sub-study and collection of blood samples for DNA and RNA. The sample for RNA, should be collected on day 1/baseline (pre-dose). Genomic DNA should be collected on day 1/baseline. If not collected at baseline, the sample for genomic DNA may be collected at any visit.
7. Sample for diagnostic assay for SARS-CoV-2 (local lab) (see Section 9.2.1.2) and RT-qPCR (NP swab; central lab) should be collected before administration of study drug. Samples for RT-qPCR (NP swab) will be collected by swabbing through both nostrils (see Section 9.2.2.1). The remnant samples may additionally be used for exploratory viral RNA sequencing and viral infectivity analyses. The requirement for a local diagnostic assay for SARS-CoV-2 may be waived if the results are not expected to be available in a timely manner for randomization.
8. Study drug should be administered after all biological samples at screening/baseline have been collected.
9. Subjects who are RT-qPCR positive at the end of the EAP will continue to have samples collected weekly (NP swab; central lab) for RT-qPCR. Subjects will continue assessments/sample collections until 2 negative RT-qPCR test results have been obtained ≥24 hours apart (all samples must be negative). Subjects who are RT-qPCR negative at the end of the EAP will have samples collected only if they become symptomatic with COVID-19 in the follow-up period. If a subject is hospitalized for suspected COVID-19, every effort should be made by the site personnel to collect, as soon as possible, a NP swab sample for central lab SARS-CoV-2 RT-qPCR testing. In subjects where it is not possible to have samples collected for assessment in the central laboratory, study site personnel will attempt to obtain and record information about all SARS-CoV-2 tests conducted in local laboratories associated with other medical facilities, including result(s), name of the assay(s) and whether the laboratory(ies) conducting the assays is a CLIA certified (or equivalent) laboratory. The positive test result should be recorded as concomitant procedures.

10. For subjects who are not in the sentinel group (subset 1; completed), vital signs will be monitored on site as follows: Safety group (subset 2; completed): at baseline predose and then every hour for 2 hours after study drug administration and a phone call on day 4 to assess AEs, specifically injection site reactions and hypersensitivity; all other subjects (subset 3): at baseline and 1 hour after study drug administration. All subjects will be advised to call the site if signs/symptoms of injection site or hypersensitivity reactions occur. If the subject experiences a true medical emergency, they should visit their local hospital ED and contact the site personnel later.
11. The investigator may perform a targeted physical exam, request an exam and/or vital signs at any time. These assessments can be performed using a clinic visit or a remote visit with the investigator or sub-investigator, or designee (ie, nurse practitioner in countries where allowed by local law).
12. For all women of childbearing potential (WOCBP) and girls at or beyond menarche, except subjects with a confirmed pregnancy. If the local urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation.
13. Samples for drug concentration and, immunogenicity, and laboratory testing will be collected based on the subject subset designation as indicated in Table 4
14. The serology test results will not be communicated to the sites. The sponsor's blinded study team will not have access to post-baseline results associated with subject identification until after the database is locked.
15. During each scheduled or unscheduled visit/contact, the investigator or designee will query subject about AEs in general (see Section 10.1.1) and evaluate if the AEs are associated with SARS-CoV-2 infection, including fever (see Section 9.2.2.2). The investigator should recommend that subjects (themselves or by their parent/guardian) measure their temperature daily during EAP, approximately at the same time, and also every time when the subject feels feverish, chills, or sick. Subjects with symptomatic SARS-CoV-2 infection should be queried on their symptoms weekly until symptoms resolve, even during follow-up period, then follow the regular schedule.
16. The information for the household assessment, including household members who receive an EUA approved monoclonal antibody treatment for COVID-19 or household members participating in the R10933-10987-COV-2067 study, should preferably be collected at the baseline visit. There will be a follow-up assessment at day 29.
17. All subjects will have a weekly NP swab sample collected during the EAP. Only subjects who are RT-qPCR positive will continue to have weekly NP swab samples collected during the follow-up period until 2 consecutive negative (≥24 hr) RT-qPCR results or the end of study visit.
18. Only for RT-qPCR positive subjects (cohort A and cohort B): Complete assessments from the time the subject first becomes RT-qPCR positive or from the time they develop symptoms suspected to be COVID-19 (later confirmed by RT-qPCR positive results) until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or until the end of study visit.

19. All subjects or parent/guardians of adolescent pediatric subjects will complete the TEAE assessment weekly during the EAP. Subjects who are RT-qPCR negative will complete the TEAE assessment monthly during the follow-up period. Subjects who have symptomatic SARS-CoV-2 infection will complete the TEAE assessment weekly during the follow-up period until the COVID-19 related symptoms resolve after which the subject will complete the TEAE assessment monthly until the end of study visit.
20. Samples will be collected only from RT-qPCR positive subjects (cohort A and cohort B) from the time the subject first becomes RT-qPCR positive until the end of study. Note: this includes subjects who have returned to RT-qPCR negative by this visit.

Table 4: Schedule of Events: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentration, Immunogenicity, and Laboratory Testing

Samples for drug concentration (dense PK, sparse PK), immunogenicity assessment (ADA), and clinical laboratory testing (hematology, blood chemistry, and urinalysis) will be collected based on subset designation using subject number (assigned by IWRS):

- **Sentinel group (Subset 1; completed)**: First 30 subjects
- **Safety group (Subset 2; completed):** 31st to 400th subject
- **All other subjects (Subset 3):** 401st to last subject

Visit	**Screening / Baseline[1]**	**Sentinel Group Only**		**Efficacy Assessment Period (EAP)**				**Follow-up Period**							**ET Visit[5]**	**Unscheduled Visit**
Site (S)	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**			
Visit Number	**1**	**2**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS 15**		
Day	1	2	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)				±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Sentinel Group (Subset 1)																
Dense PK[2]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Blood chemistry[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Urinalysis[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Safety group (Subset 2)																
Sparse PK[2]	X[1]						X	X		X		X		X	X	X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]						X	X	X	X	X	X	X	X	X	
Blood chemistry[4]	X[1]						X	X	X	X	X	X	X	X	X	
Urinalysis[4]	X[1]						X	X	X	X	X	X	X	X	X	
All other subjects (Subset 3)																
PK[2]																X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]						X									
Blood chemistry[4]	X[1]						X									
Urinalysis[4]	X[1]						X									

ADA, anti-drug antibodies; EAP, Efficacy assessment period; EOS, end of study; ET, Early termination; PK, Pharmacokinetics

9.1.2. Schedule of Events Table 4: All Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentrations, Immunogenicity, and Laboratory Testing

1. Samples should be collected before the administration of study drug. Administration of study drug must be performed on the on same day as sample collection.
2. Actual dosing time and dense PK, sparse PK, and ADA sample collection times will be recorded.
3. At the screening/baseline visit, the window for baseline pre-dose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
4. Whole blood samples for hematology and blood chemistry and urine samples for urinalysis will be analyzed at central lab.
5. Subjects who prematurely discontinue the study should have sample collection listed in the ET visit before exiting the study.
6. A PK serum sample and an ADA serum sample will be collected as soon as possible or within 7 days of receiving the first positive SARS-CoV-2 RT-qPCR result for cohort A subjects. The ADA serum samples may be analyzed for ADA and NAb, if feasible.
7. A PK serum sample and an ADA serum sample will be collected as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

Table 5: Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive)

Visit	Screening / Baseline[1]	Additional Safety (Sentinel Only)[2]				Efficacy Assessment Period (EAP)[3]				Follow-up Period							ET	Unscheduled Visit[4]
Visit Location Site (S), Phone (P)[5]	**S**	**S**	**S**	**P[5]**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**		
Visit Number	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS**		
Day	1	1	2	3	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)						±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Screening/Baseline:																		
Inclusion/exclusion	X																	
Informed consent (parent/guardian)/pediatric assent (subject)	X																	
Informed consent(adults or parent/guardian)/pediatric assent for PGx sub-study(optional)[19]	X																	
Medical history	X																	
Demographics and risk factors for SARS-CoV-2 infection	X																	
Household assessment	X[15]								X									
Appropriate sample, diagnostic assay for SARS-CoV-2 (local lab)	X[6]																	
Randomization	X																	
Treatment:																		
Study drug administration	X[7]																	
Efficacy (Virology):																		
NP swab, SARS-CoV-2 RT-qPCR (central lab)[6,16]	X[7]					X	X	X	X	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X	X
Efficacy (Subject-Reported) only for RT-qPCR positive subjects:																		
Assessment of ED, UCC, hospital visits[17]						X	X	X	X	X	X	X	X	X	X	X		
Absenteeism assessment[17]						X	X	X	X							X		
Safety:																		
Vital signs	X[2,10]	X[2]							X							X		X
Targeted PE[10]	X		X		X				X							X		X
Adverse events[14,18]	X[9]	X[2]	X[2]	X[2]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds, Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test for WOCBP (dipstick, local lab)[11]	X															X	X	
Laboratory Testing[12]:																		
Clinical Laboratory, Hematology, Blood Chemistry	Refer to Table 6																	
Pharmacokinetics and Immunogencity[12]:																		
Drug concentration / Anti-drug antibodies (ADA)	Refer to Table 6																	
Biomarkers:																		
Serum for serology (central lab)[12,13]	Refer to Table 6																	
Pharmacogenomics Sub-Study:																		
Whole Blood for RNA (Optional)[12,19]	Refer to Table 6																	
Whole Blood for DNA (Optional)[12,19]	Refer to Table 6																	

EAP, Efficacy assessment period; EOS, end of study; ED, emergency departments; ET, Early termination; UCC, urgent care centers; PE, physical exam; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

9.1.3. Schedule of Events Table 5 Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Footnotes

1. The screening visit and baseline visit should both occur on the same day. If needed, a remote visit may occur to sign the ICF and collect medical history and concomitant medication use, on the day prior to, but within 24 hours of study drug administration, so that the in-person screening and randomization visit may be abbreviated, due to COVID-19 considerations. Study drug administration must occur within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.

2. The pediatric sentinel group (subset 4) (see Section 6.1.2) will have additional safety monitoring on day 1 and through day 4.

   Vital signs: On day 1, vital signs (pulse rate, respiratory rate, body temperature and blood pressure [if feasible, according to the child's age]) will be measured at predose, approximately every 30 minutes during the first 2 hours after dose before dismissal.

   Adverse Events (injection site reactions and hypersensitivity): after the administration of the first dose of study drug, subjects will be monitored on site for a minimum of 2 hours and then by daily visits to the study site or phone calls for the first 4 days (96 hours), particularly focusing on the assessment of injection site reactions and hypersensitivity after study drug administration.

3. Pediatric subjects who have a positive RT-PCR result during screening, or who have a positive RT-qPCR result any time after screening, will have the additional assessments done as indicated (**RT-qPCR positive pediatric subjects only**). A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A1 pediatric subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all pediatric subjects.

   For pediatric subjects who become RT-qPCR positive after screening, the visit schedule will proceed as follows: (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

4. Unscheduled visits: If, at any time after randomization until end of study, a pediatric subject develops fever, an acute respiratory illness or other symptoms they may feel could be related to COVID-19 or is hospitalized for suspected COVID-19, the pediatric subject and/or parent/guardian should alert the investigator or designee immediately who will assess the subject's symptoms and condition (can be performed by phone contact, telemedicine, online meeting, home health care, etc) to decide if the pediatric subject should have an unscheduled visit for collection of NP swab sample for RT-qPCR testing.

The pediatric subject and/or parent/guardian may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1). The investigator or designee should query the subject and/or parents/guardians about AEs in general and AEs consistent of COVID-19 and record the information on CRF (see detailed description of the procedure in Section 9.2.2.2).

(a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

5. Visit may occur by phone or electronic means
6. Sample for diagnostic assay for SARS-CoV-2 (local lab) (see Section 9.2.1.2) and RT-qPCR (NP swab; central lab) should be collected before administration of study drug. Samples for RT-qPCR (NP swab) will be collected by swabbing a single nostril (see Section 9.2.2.1). The remnant samples may additionally be used for exploratory viral RNA sequencing and viral infectivity analyses. The requirement for a local diagnostic assay for SARS-CoV-2 may be waived if the results are not expected to be available in a timely manner for randomization.
7. Study drug should be administered after all biological samples at screening/baseline have been collected.
8. Pediatric subjects who are RT-qPCR positive at the end of the EAP will continue to have samples collected weekly (NP swab; central lab) for RT-qPCR. Pediatric subjects will continue assessments/sample collections until 2 negative RT-qPCR test results have been obtained ≥24 hours apart (all samples must be negative). Subjects who are RT-qPCR negative at the end of the EAP will have samples collected only if they become symptomatic with COVID-19 in the follow-up period.
9. All other pediatric subjects (subset 5) will have additional safety monitoring on day 1 at baseline and 1 hour after study drug administration. All pediatric subjects or their parent/guardian will be advised to call the site if signs/symptoms of injection site or hypersensitivity reactions occur. If the pediatric subject experiences a true medical emergency, they and their parent/guardian should visit their local hospital ED and contact the site personnel later.
10. The investigator may perform a targeted physical exam, request an exam and/or vital signs at any time. These assessments can be performed using a clinic visit or a remote visit with the investigator or sub-investigator, or designee (ie, nurse practitioner in countries where allowed by local law).
11. For all girls at or beyond menarche. If the local urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation.

12. Samples for drug concentration, immunogenicity, laboratory testing, serology, and pharmacogenomics sub-study will be collected based on the pediatric subject subset designation as indicated in Table 6.
13. The serology test results will not be communicated to the sites. The sponsor's blinded study team will not have access to post-baseline results associated with pediatric subject identification until after the database is locked.
14. During each scheduled or unscheduled visit/contact, the investigator or designee will query the pediatric subject and/or parent/guardian about AEs in general (see Section 10) and evaluate if the AEs are associated with SARS-CoV-2 infection (see Section 9.2.2.2). Pediatric subjects and/or parent/guardian with symptomatic SARS-CoV-2 infection should be queried on their symptoms weekly until symptoms resolve, even during follow-up period, then follow the regular schedule.
15. The information for the household assessment, including household members who received EUA approved monoclonal antibody treatment for COVID-19 or household members participating in the R10933-10987-COV-2067 study should preferably be collected at the baseline visit. There will be a follow-up assessment at day 29.
16. All pediatric subjects will have a weekly NP swab sample collected during the EAP. Only pediatric subjects who are RT-qPCR positive will continue to have weekly NP swab samples collected during the follow-up period until 2 consecutive negative (≥24 hr) RT-qPCR results or the end of study visit.
17. Only for RT-qPCR positive subjects (cohort A1 and cohort B1): Complete assessments from the time the subject first becomes RT-qPCR positive or from the time they develop symptoms suspected to be COVID-19 (later confirmed by RT-qPCR positive results) until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or until the end of study visit.
18. All pediatric subjects and/or parent/guardian will complete the TEAE assessment weekly during the EAP. Subjects who are RT-qPCR negative will complete the TEAE assessment monthly during the follow-up period. Pediatric subjects and/or parent/guardian who have symptomatic SARS-CoV-2 infection will complete the TEAE assessment weekly during the follow-up period until the COVID-19 related symptoms resolve after which the pediatric subject and/or parent/guardian will complete the TEAE assessment monthly until the end of study visit.
19. Separate consent (parent/guardian of pediatric subject)/pediatric assent is required for participation of pediatric subjects who weigh ≥10 kg in the optional genomic sub-study and collection of blood samples for DNA and RNA.

Table 6: Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing

Samples for drug concentration (PK), immunogenicity assessment (ADA), and clinical laboratory testing (hematology, blood chemistry, and serology) will be collected based on subset designation and sample schedule (A, B, C, D) using subject number (assigned by IWRS):

- **Pediatric sentinel group (Subset 4)**: First 12 pediatric subjects (4 subjects per weight group (≥20 kg; 10 kg to <20 kg; <10 kg)
- **All other pediatric subjects (Subset 5):** All other pediatric subjects

Visit	**Screening / Baseline[1]**	**Sentinel Group Only**	**Efficacy Assessment Period (EAP)**			**Follow-up Period**							**ET Visit[5]**	**Unscheduled Visit**
Site (S)	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**			
Visit Number	**1**	**2**	**5**	**6**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS 15**		
Day	1	2	8	15	29	57	85	113	141	169	197	225		
Week	0	0	1	2	4	8	12	16	20	24	28	32		
Window (day)		+2	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Sentinel Group (Subset 4)														
PK-ADA[2,3,9]; Hematology[4]; Blood Chemistry[4], Serology[4,8]														
Schedule A	X[1,8]	X			X[8]								X	X[6,7]
All other subjects (Subset 5)														
PK-ADA[2,3,9]; Hematology[4], Blood Chemistry[4], Serology[8]														
Schedule A	X[1,8]	X			X[8]								X	X[6,7]
Schedule B	X[1,8]		X		X[8]								X	X[6,7]
Schedule C	X[1,8]			X	X[8]								X	X[6,7]
Schedule D	X[1,8]				X[8]			X[8]					X	X[6,7]
Pharmacogenomics Sub-Study (only subjects ≥10 kg)														
Whole Blood for RNA (Optional)	X[10]													
Whole Blood for DNA (Optional)	X[10]													

ADA, anti-drug antibodies; EAP, Efficacy assessment period; EOS, end of study; ET, Early termination; PK, Pharmacokinetics

9.1.4. Schedule of Events Table 6: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing

1. Samples should be collected before the administration of study drug. Administration of study drug must be performed on the on same day as sample collection.
2. Actual dosing time and sample collection times will be recorded for PK-ADA samples.
3. At the screening/baseline visit, the window for baseline pre-dose PK-ADA sample collection is as close to administration of study drug as is reasonable.
4. Whole blood samples for hematology and blood chemistry will be analyzed at central lab.
5. Pediatric subjects who prematurely discontinue the study should have sample collection listed in the ET visit before exiting the study.
6. A PK-ADA serum sample will be collected as soon as possible or within 7 days of receiving the first positive SARS-CoV-2 RT-qPCR result for cohort A pediatric subjects.
7. A PK-ADA serum sample will be collected as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all pediatric subjects.
8. Serum samples for serology will be collected at baseline and day 29. For pediatric subjects <10 kg, the serum sample for serology on the day 29 visit will not be collected due to restrictions in total blood volumes collection. For pediatric subjects <3 kg, the serum sample for serology on the baseline and day 29 visit will not be collected due to restrictions in total blood volumes collection.
9. The PK-ADA serum samples may be analyzed for ADA and NAb, if feasible.
10. Only for pediatric subjects who weigh ≥10 kg: The whole blood sample for RNA, should be collected on day 1/baseline (pre-dose). The whole blood for genomic DNA should be collected on day 1/baseline. If not collected at baseline, the sample for genomic DNA may be collected at any visit.

9.1.5. Early Termination Visit

Subjects who are withdrawn from the study will be asked to provide final blood samples for drug concentration and immunogenicity analysis.

9.1.6. Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, for SARS-CoV-2 RT-qPCR and serology testing when subjects experience symptoms consistent with SARS-CoV-2 infection (per the broad-term list specified in Section 9.2.2.2), or for any other reason, as warranted.

9.2. Study Procedures

This section describes the procedures and collections that will be performed in this study. Procedures and collections will occur according to the schedule of events (Table 3 and Table 4).

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: demographics (eg, age, sex, race, weight, height, etc), medical history, local diagnostic assay for SARS-CoV-2, query for risk factors for SARS-CoV-2 infection (eg, first responder or healthcare worker; presence in outdoor or indoor crowed or public places [without keeping distance >6 feet] in the last 14 days, with or without a mask and/or eye protection; attendance to any social events with more than 10 people in the last 14 days, with or without a mask and/or eye protection; exposure to someone believed to have COVID-19; exposure to someone diagnosed with COVID-19; receipt of influenza vaccine as of July 2020), and household assessment in which subjects will be asked to provide general information about the household members (including their general demographic information, COVID-19 status, their risk of exposure to COVID-19, and treatment with an EUA approved monoclonal antibody treatment for COVID-19).

9.2.1.1. Informed Consent

Informed consent (adults and parents/guardians) and pediatric assent must be obtained according to the requirements described in Section 13.2. Optional informed consent may be obtained for participation in the pharmacogenomics sub-study (refer to Section 9.2.7 for more information on this sub-study or inclusion in the R10933-10987-COV-2067 study).

9.2.1.2. Local Diagnostic Assay for SARS-CoV-2

The investigator or sub-investigator will verify that the subjects tests negative or positive by a local diagnostic assay for SARS-CoV-2 (eg, molecular assay such as RT-PCR assay for SARS-CoV-2 or a SARS-CoV-2 antigen test using an appropriate sample such as NP, nasal, OP, or saliva). The local diagnostic assay for SARS-CoV-2 must be considered acceptable for clinical use by local standards. If the test has not been approved or received EUA issued by the US FDA or by the equivalent local health authority, then the Sponsor should be consulted. The use of a RT-PCR assay is highly recommended.

The local diagnostic test result, specimen type (eg, nasal swab), assay type, and date of test will be recorded in the CRF. The sample type collected is dependent on local lab requirements.

9.2.2. Efficacy Procedures

9.2.2.1. Nasopharyngeal Swab SARS-CoV-2 RT-qPCR Test (Central Lab)

Nasopharyngeal swab sample will be collected from subjects to determine presence or absence of SARS-CoV-2 virus and to determine the relative quantification of viral load. For adult and adolescent subjects (≥12 years of age), NP swab samples will be collected by swabbing through both nostrils on all planned timepoints (Table 3). For pediatric subjects (<12 years of age), NP swab samples will be collected by swabbing through a single nostril on all planned timepoints

(Table 5). Detailed instructions for sample collections are in the laboratory manual provided to study sites.

9.2.2.2. COVID-19 Symptomology (Strict Terms, Broad Terms, and CDC Definition)

During each scheduled or unscheduled visit/contact, the investigator or sub-PI investigator, or designee (ie, nurse practitioner in countries where allowed by local law) will query the subject and/or subject's parent or guardian about adverse events the subject is experiencing or has experienced since the last visit/contact (eg, within the prior week if it is a weekly scheduled visit) and ask about all of the signs and symptoms associated with these adverse events including the start date, end date and severity of each. The investigator should avoid querying the subject and/or subject's parent or guardian by running a check-list of signs and symptoms, but rather allow the subject and/or subject's parent or guardian to spontaneously report everything that they presented.

All signs and symptoms related to the AEs, along with the corresponding start date, end date and severity should be documented in the subject's medical records (source document). As signs and symptoms may appear and resolve on different days and may precede or occur after the collection of NP swab sample for the SARS-CoV-2 RT-qPCR test, it is important that this detailed information be captured in the source document.

Independent of the results (positive or negative) of the SARS-CoV-2 RT-qPCR tests performed on samples collected from study subjects during the weekly or unscheduled visits, all adverse events must be documented in the AE CRF. Signs and symptoms related to the adverse events reported in the AE CRF and confirmed to be temporally related to a positive SARS-CoV-2 RT-qPCR test collected from the subject's NP swab sample will be reported on a separate CRF (individual sign or symptom with start date and end date, and associated severity).

For the purpose of the study's primary and secondary objectives, the assessment of association of symptomatic disease with SARS-CoV-2 infection (ie, diagnosis of strict term COVID-19, broad term COVID-19, and CDC definition of COVID-19) will be based on the strict term, broad term, and CDC COVID-19 definitions described below (Table 7) and the temporal relationship of the signs and symptoms with lab confirmed SARS-CoV-2 infection (based on central lab RT-qPCR test result).

Temporal Relationship of Signs and Symptoms with Positive RT-qPCR for Diagnosis of COVID-19

The onset date of signs/symptoms will utilize a ±14 days window from the date of the positive SARS-CoV-2 RT-qPCR, so long as the signs/symptom onset does not precede a negative SARS-CoV-2 RT-qPCR test. That is, the onset date of symptomatic SARS-CoV-2 infection is defined as the date of the first sign/symptom that is consistent with a diagnosis of COVID-19 as determined by the investigator. The onset date must be after the last negative SARS-CoV-2 RT-qPCR and no more than 14 days prior to the first positive SARS-CoV-2 RT-qPCR or must occur on or before 14 days after the last positive SARS-CoV-2 RT-qPCR.

Definitions of COVID-19 Signs and Symptoms used for the Secondary Efficacy Endpoints:

1. **Strict term:** as described in Section 4.1.2 and Section 4.2.2 , a secondary endpoint will utilize a strict definition of signs and symptoms of COVID-19 (see Table 7).

2. **Broad term:** as described in Section 4.1.2 and Section 4.2.2, a secondary endpoint will utilize a broad term COVID-19 signs and symptoms defined as any of the 23 symptoms listed in Table 7 or fever (≥38°C).
3. **CDC definition:** as described in Section 4.1.2 and Section 4.2.2, a secondary endpoint will utilize the CDC COVID-19 2020 Interim Case Definition (approved 5 Aug 2020) (see Table 7) to allow for comparability across studies in the field (CDC, 2020a).

Table 7: Strict-Terms, Broad-Terms, and CDC Definition COVID-19 Signs and Symptoms

Strict-term defined by:	Broad-term defined as any of the following:	CDC definition
Fever (≥38°C) PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath) *OR* 2 respiratory symptoms (sore throat, cough, shortness of breath) *OR* 1 respiratory symptom (sore throat, cough, shortness of breath) PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise)	Fever ≥38°C • The signs and symptoms below: 1. Feverish 2. Sore throat 3. Cough 4. Shortness of breath/difficulty breathing *(nasal flaring*)* 5. Chills 6. Nausea 7. Vomiting 8. Diarrhea 9. Headache 10. Red or watery eyes *(conjunctivitis)* 11. Body aches such as muscle pain or joint pain *(myalgia, arthralgia)* 12. Loss of taste/smell 13. Fatigue *(fatigue or general malaise or lethargy*)* 14. Loss of appetite or poor eating/feeding 15. Confusion 16. Dizziness 17. Pressure/tightness in chest 18. Chest pain 19. Stomach ache (abdominal pain*) 20. Rash 21. Sneezing 22. Runny nose 23. Sputum/phlegm Other **Signs and symptoms observed in pediatric subjects*	At least 2 of the following symptoms: fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion or runny nose OR Any 1 of the following symptoms: cough, shortness of breath, difficulty breathing, new olfactory disorder, new taste disorder OR Severe respiratory illness with at least 1 of the following, clinical or radiographic evidence of pneumonia, ARDS.

9.2.2.3. Assessment of Medically Attended Visits

Only for RT-qPCR positive subjects (cohort A, cohort A1, cohort B, and cohort B1): Subjects and/or their parent/guardian (as appropriate) who are or become SARS-CoV-2 RT-PCR positive will be queried on any SARS-CoV-2 infection-related medically attended visits to the ED, UCC, or hospitalization (Table 3 and Table 5). The assessment of medically attended visits to ED, UCC or hospitalization will be performed from the time the subject first becomes SARS-CoV-2 RT-qPCR positive or from the time they develop symptoms suspected to be COVID-19 (later confirmed by RT-qPCR positive results) until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or until the end of study visit. Details associated with any SARS-CoV-2 infection-related medically-attended visit will be recorded and will include at minimum:

- Nature of the visit (ED, UCC, hospital stay)
- Date and length of visit
- Primary reason for the visit should be recorded as an adverse event
- Assessment of the following parameters or occurrences (worst or most abnormal finding) during the medically attended visit/stay:
  - Abnormal vital signs: respiratory rate ≥30 per minute, heart rate ≥125 per minute, peripheral capillary oxygen saturation (SpO2) ≤93% on room air at sea level, or oxygen partial pressure (PaO2)/fractional inspired oxygen (FiO2) <300 mm Hg) *Note: these limits for abnormal vital signs are for adult and adolescent subjects.*
  - Respiratory failure: needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, extracorporeal membrane oxygenation (ECMO)
  - Evidence of shock: systolic blood pressure (SBP) <90 mm Hg, diastolic blood pressure (DBP) <60 mm Hg, or requiring vasopressors *Note: these limits for abnormal vital signs are for adult and adolescent subjects.*
  - Multiorgan dysfunction: Significant acute renal, hepatic, or neurologic dysfunction
  - Multisystem inflammatory syndrome in children (MIS-C) *Note: for pediatric subjects <18 years only*
  - Admission to an ICU

9.2.2.4. Absenteeism Assessment

Only for RT-qPCR positive subjects (cohort A, cohort A1, cohort B, and cohort B1): Subjects and/or their parent/guardian who are or become SARS-CoV-2 RT-PCR positive during the EAP will be queried on any SARS-CoV-2 infection-related absenteeism (Table 3 and Table 5). Absenteeism is defined as number of days missed for daily responsibilities, including work (employed adults) or school (students), daycare, or family obligations/responsibilities (childcare or eldercare). The assessment of absenteeism will be performed from the timepoint the subject first becomes SARS-CoV-2 RT-qPCR positive until the end until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or until the end of study visit.

9.2.3. Safety Procedures

9.2.3.1. Targeted Physical Examination and Vital Signs

The targeted physical examination and vital signs include measurements of temperature, blood pressure (measured after the subject has been resting quietly for at least 5 minutes and may be obtained from a seated or supine position), pulse rate, and respiratory rate, and examination of the oropharynx, skin, heart, lungs and any other system(s) depending on any complaints or concerns expressed by the subjects.

Vital signs consisting of blood pressure, pulse rate, body temperature, and respiratory rate will be collected pre-dose and after dose administration as follows:

- **Sentinel group (subset 1; completed):** approximately every 30 minutes during the first 2 hours after study drug administration, at hour 3, and at hour 4 before dismissal.
- **Safety group (subset 2; completed)**: approximately every hour for 2 hours after study drug administration.
- **All other adult and adolescent subjects (subset 3)**: approximately 1 hour after study drug administration.
- **Pediatric sentinel group (subset 4):** approximately every hour for at least 2 hours after study drug administration (blood pressure will be measured, if feasible, according to the child's age).
- **All other pediatric subjects (subset 5):** approximately 1 hour after study drug administration (blood pressure will be measured, if feasible, according to the child's age).

9.2.3.2. Laboratory Testing

Samples for laboratory testing will be collected at visits according to the Schedule of Events Table 4 and Table 6. Samples will be analyzed by a central laboratory. For pediatric subjects (<18 years) only, a numbing cream may be used for blood sample collection. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

Urine pregnancy test will be performed for WOCBP at baseline and prior to administration of study drug. If a subject has a positive urine pregnancy test, a serum pregnancy test should be performed to confirm.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment **may** be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Drug Concentration and Measurements

Serum samples for REGN10933 and REGN10987 drug concentration measurement will be collected per the schedule of events for adult and adolescent subjects (Table 4) and pediatric subjects (<12 years of age) (Table 6). For pediatric subjects (<18 years) only, a numbing cream may be used for blood sample collection.

A subset of the first 30 adult subjects (by subject number by IVRS) will have frequent sample collection (dense PK). The second subset will include the next 370 adult subjects (the 31st to 400th subjects) who will have less frequent sample collection (sparse PK). Pediatric subjects will have 3 serum samples collected. In order to collect serum samples over the study duration, pediatric subjects will be assigned by IVRS to 1 of 4 sampling schedules (A, B, C, D) (Table 6). Any unused samples may be kept for up 15 years (or for a shorter time period if required per regional laws and regulations) after study completion for use in exploratory research.

9.2.5. Immunogenicity Measurements and Samples

Immunogenicity will be assessed by ADA and NAb. Samples for ADA and NAb assessment will be collected for adult and adolescent subjects (<12 years) at time points listed in Table 4. Samples will be assessed for ADA and NAb using samples collected for subjects (<12 years) at the time points listed in Table 6, if feasible. For pediatric subjects (<18 years) only, a numbing cream may be used for blood sample collection. Any unused samples may be kept for up 15 years (or for a shorter time period if required per regional laws and regulations) after study completion for use in exploratory research.

9.2.6. Exploratory Pharmacodynamic/Biomarker Procedures

A description of planned or potential exploratory analyses is provided below. Samples for assessment of pharmacodynamic and exploratory biomarkers will be collected from adult and adolescent subjects at time points indicated in Table 4. Sample for serological assays will be collected from pediatric subjects (<12 years) at the time points indicated in Table 6. For pediatric subjects (<18 years) only, a numbing cream may be used for blood sample collection. Residual serum or plasma samples collected for other purposes may also be used to study how REGN10933+REGN10987 work and SARS-CoV-2 infection, including but not limited to, cytokines, complement pathways, and other factors emerging to be associated with disease or clinical prognosis. Any unused samples may be kept for up 15 years (or for a shorter time period if required per regional laws and regulations) after study completion for use in exploratory research.

9.2.6.1. Virology

9.2.6.1.1. Viral Sequencing

In support of public health initiatives to track SARS-CoV-2 genetic variants, viral genome sequencing will be performed on all viral nucleic acid isolated from NP swab samples at baseline. Sequencing analyses will be of the entire viral genome, including the full gene sequence that encodes the SARS-CoV-2 S protein.

The results of the viral sequencing will not be included in the clinical study report.

9.2.6.1.2. Viral Resistance

Subjects will be assessed for virologic resistance, defined as (1) those subjects who are positive at baseline and remain positive without a consistent decrease in viral load by 4 weeks, (2) those subjects who were negative and become positive during the EAP, and/or (3) those subjects who have 2 consecutive negative RT-qPCR tests with a subsequent positive RT-qPCR test result. For subjects who exhibit viral resistance, viral sequencing will be performed to understand the potential relationship between genetic mutations and mAb functional activity. Viral sequencing may also be done on a gender-matched placebo control group in order to determine whether any genetic mutations observed in the mAb treatment group are naturally emergent genetic variants.

The results of the viral resistance will not be included in the clinical study report.

9.2.6.1.3. Viral Infectivity

To explore the effects of REGN10933+REGN10987 on infectivity of SARS-CoV-2, we may use viral culture assays or sub genomic viral mRNA transcript analyses. Subgenomic viral RNA transcripts potentially indicate the presence of actively replicating virus in samples, as viral subgenomic mRNA is transcribed only in infected cells and is not packaged into virions. These data may be associated to RT-qPCR data from matched samples for each group and compare to placebo or other clinical or other measures in the study.

9.2.6.2. Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies

In order to assess the impact of baseline humoral immunity/antibody response to SARS-CoV-2 on REGN10933+REGN10987 efficacy to prevent SARS-CoV-2 infection, serum anti-SARS-CoV-2 will be measured at baseline, including but not limited to those which detect antibodies against the S protein and/or the N protein and/or neutralization assays. The impact of a positive serology result on drug efficacy will be assessed by associating seropositivity to positive SARS-CoV-2 RT-qPCR test from NP swabs. Association of seropositivity with clinical endpoints and other measures may also be explored.

To explore whether REGN10933+REGN10987 affect the generation of a humoral immune response to SARS-CoV-2, serum anti-SARS-CoV-2 N protein antibodies will be measured using immunoassays in REGN10933+REGN10987 groups as compared to placebo control, as well as to baseline.

Any unused samples may be kept for up 15 years after study completion for use in exploratory research (or for a shorter time period if required per regional laws and regulations).

9.2.6.3. Serum and Plasma for Research

Research serum and plasma are being collected and banked for exploratory research related to COVID-19, SARS-CoV-2, REGN10933+REGN10987, host and viral biological pathways and mechanisms related disease activity and clinical outcomes. The data from these exploratory analyses may not be included in the CSR.

9.2.7. Pharmacogenomic Analysis (Optional)

Adult and pediatric subjects (<18 years and ≥10 kg) who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Blood sample for RNA must be collected predose on day 1. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose) but can be collected at a later study visit. For pediatric subjects (<18 years and ≥10 kg) only, a numbing cream may be used for blood sample collection. DNA and RNA samples will be collected for pharmacogenomics analyses to understand the genetic and/or transcriptional determinants of efficacy and safety associated with the treatments in this study and the molecular basis of SARS-CoV-2 infection. These samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the Sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN10933+REGN10987, other SARS-CoV-2 infection clinical outcome measures, and possible treatment-emergent adverse events. In addition, associations between genomic variants and prognosis or progression of SARS-CoV-2 infection as well as related viral pneumonia and respiratory diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic and transcriptional markers related to the study drug, target pathway, or SARS-CoV-2 infection. These data may also be combined with viral sequence analyses to study host/virus genetic interactions.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period.

Results from the genomic and transcriptional analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of study (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or adolescent subject's parent or guardian, or by questioning the subject or the adolescent subject's parent or guardian at each study visit. Subjects or the subject's parent or guardian should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator should recommend that subjects (themselves or by their parent/guardian) measure their temperature daily during efficacy assessment period, approximately at the same time, and also every time the subject feels feverish, chills, or sick. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow-up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the Investigator assesses as related to study drug should also be reported.

All AEs, serious adverse events (SAEs), AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following: (as defined in Section 10.2.3):
  - Grade 3 or greater injection site reactions or hypersensitivity reactions including but not limited to anaphylaxis, laryngeal/pharyngeal edema, severe bronchospasm, chest pain, seizure, or severe hypotension (AE grading system is provided in Section 10.2.4)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study subject existing at the time of signing the informed consent form, during the study, and for 8 months following administration of the single dose of study drug. Any complication of pregnancy affecting a female study subject and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a subject administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a subject is a passenger).
- Is **life-threatening** – in the view of the investigator, the subject is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-subject **hospitalization** or **prolongation of existing hospitalization**. In-subject hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Severity

The severity of AEs (including test findings classified as AEs) and injection-site -related reactions will be graded using the current version of the NCI–CTCAE v5.0 0 (DCTD, 2017). The NCI-CTCAE severity grading systems for anaphylaxis, allergic reaction, and injection site reaction are specifically provided Table 8.

Table 8: NCI-CTCAE Severity Grading System for Adverse Events for Anaphylaxis, Allergic Reaction, and Injection Site Reaction

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			only grade 3, 4, and 5 are reportable as AESI for R10933-10987-COV-2069[a]		
Anaphylaxis[b]	Not applicable	Not applicable	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Allergic reaction (hypersensitivity reaction)[c]	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Injection site reaction[d]	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

[a] See details in Section 10.1.3

[b] Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death

[c] Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.

[d] Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.

Source: (DCTD, 2017)

10.2.5. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

For double blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Subject's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, subject's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, subject's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure, and cannot be reasonably explained by the nature of the reaction, subject's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure, or can be reasonably explained by the nature of the reaction, subject's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study subject at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Pharmacovigilance; Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, IRBs/ECs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (REGN10933+REGN10987), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (REGN10933+REGN10987) is assessed against the Reference Safety Information section of the IB that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report to health authorities and IRBs/ECs as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the SAP for the study. The SAP will be revised prior to the end of the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

The following null and alternate hypotheses will be tested for the primary and secondary efficacy endpoints:

H0: There is no treatment difference between REGN10933+REGN10987 and placebo

H1: There is a treatment difference between REGN10933+REGN10987 and placebo

11.2. Justification of Sample Size

An administrative assessment for assumption verification and sample size estimation for cohort A was conducted using unblinded descriptive analyses without performing any formal statistical hypothesis testing. Analyses were conducted in the group of cohort A subjects randomized from study initiation through the date of randomization that was associated with approximately 30 RT-PCR events amongst cohort A seronegative subjects during the EAP (subjects overall regardless of baseline serology status [eg, seronegative, seropositive, or other]). The subjects who were evaluated in this descriptive analysis will not be included for the final efficacy analyses, however, these subjects will be included in the safety analyses (Section 11.4.9). To maintain operational efficiencies and because of the progressive rollout of SARS-CoV-2 vaccination which may change the dynamics of virus transmission/infection in the near future, enrollment into the study was not paused while the administrative assessment was performed and was estimated that the total enrollment may reach approximately 3500 subjects. The justification of sample size in cohort A (Section 11.2.1) with the assumption of reduction of symptomatic infection is based on the results from the administrative assessment.

11.2.1. Cohort A: Adult and Adolescent Subjects (≥12 years) Who Are SARS-CoV-2 RT-qPCR Negative at Baseline

In cohort A, subjects are randomized in a 1:1 allocation ratio to REGN10933+REGN10987 or placebo. The primary hypothesis is the reduction in the proportion of symptomatic RT-qPCR (broad-term) confirmed SARS-CoV-2 infections in seronegative subjects. To calculate the sample size required to achieve at least 90% power for seronegative subjects in cohort A, it is assumed that the statistical hypothesis will be tested in a 2-sided test. Based on the administrative assessment results among 409 seronegative subjects in cohort A, a 50% reduction of infections (symptomatic or asymptomatic) compared to the placebo group and a 100% reduction of symptomatic infections compared to placebo group was observed. Due to the small sample size in the administrative assessment, it is assumed, for the purpose of calculating study power, that an approximately 50% reduction or greater in symptomatic infections compared to placebo group will be expected for the final primary efficacy analysis.

In this household study design, the number of subjects per household, the correlation between subjects and symptomatic infection rates within a household are unknown. To detect a relative risk of 0.5 (ie, 50% reduction of the assumed 10% attack rate in the placebo arm), equivalent to an odds ratio of 0.47, power was calculated compared to the p-value of 0.05 based on 2000 simulations in 1248 subjects from 430 households (ie, assuming an average household size of 2.9 seronegative subjects). Table 9 provides power calculations by varying degrees of correlation within household. In all cases, the power of the study is >90% using a generalized linear model with the generalized estimation equation (GEE) approach and assuming a compound symmetry covariance matrix.

Table 9: Simulated Power for Household Design (1248 Subjects over 430 Households)

Placebo Attack Rate	REGN10933+ REGN10987 Attack Rate	Correlation within Household	Average Odds Ratio REGN10933+REGN10987 versus Placebo	Power
10%	5%	0.1	0.485	0.914
10%	5%	0.2	0.485	0.934
10%	5%	0.3	0.480	0.956
10%	5%	0.4	0.481	0.972
10%	5%	0.5	0.476	0.983
10%	5%	0.6	0.478	0.999

At least 1980 subjects will need to be enrolled in cohort A to have a minimum of 1248 seronegative subjects, assuming that 10% of subjects drop out and 30% of subjects are seropositive at baseline.

11.2.1.1. Cohort A1: Pediatric Subjects (<12 years) Who Are SARS-CoV-2 RT-qPCR Negative at Baseline

Approximately up to a total of 250 pediatric subjects (<12 years) will be enrolled in this study. Of the 250 subjects, 90% (225/250) are expected to be enrolled in this cohort (ie, central lab RT-qPCR negative at baseline) for evaluation of the drug concentration and exposure, and safety. The actual number of subjects in this cohort will depend on the actual percentage of subjects with a baseline negative RT-qPCR enrolled. No statistical hypothesis tests will be performed.

11.2.2. Cohort B: Adult and Adolescent Subjects (≥12 years) Who Are SARS-CoV-2 RT-qPCR Positive at Baseline

The primary endpoint in asymptomatic, seronegative subjects in cohort B is the proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR test result at baseline or during the EAP.

The sample size of cohort B is based on the frequency of finding positive subjects while enrolling cohort A and assumes that approximately 10% of subjects in a household are already positive for SARS-CoV-2 by RT-qPCR at baseline. Among approximately 3500 adult and adolescent subjects that are anticipated to be enrolled in cohort A or cohort B, the number of subjects expected in cohort B is approximately 220, including 200 seronegative subjects. Assuming that 50% of infected placebo subjects at baseline will develop symptoms, 200 seronegative subjects in cohort B will provide >90% power to detect a relative risk of 0.5 using a 2-sided Fisher's exact test at an alpha level of 0.05.

11.2.2.1. Cohort B1: Pediatric Subjects (<12 years) Who Are SARS-CoV-2 RT-qPCR Positive at Baseline

Approximately up to a total of 250 pediatric subjects (<12 years) will be enrolled in this study. Of the 250 subjects, 10% (25/250) are expected to be enrolled in this cohort (ie, central lab RT-qPCR positive at baseline) for evaluating the drug concentration and exposure, and safety. No statistical hypothesis tests will be performed. The actual number of subjects in this cohort will depend on the actual percentage of subjects with a baseline positive RT-qPCR enrolled. No statistical hypothesis tests will be performed.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

Seronegative Modified Full Analysis Set (Seronegative mFAS-A) - Cohort A

The seronegative modified full analysis set for cohort A (seronegative mFAS-A) includes all randomized subjects aged 12 years and older who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects included in the administrative assessment analysis are excluded from the seronegative mFAS-A population.

Subjects will be analyzed based on the randomized treatment assignment. The seronegative mFAS-A population is the primary analysis population for the primary and secondary endpoints for cohort A of this study unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-A1) - Cohort A1

The seronegative modified full analysis set for cohort A1 (seronegative mFAS-A1) includes all randomized subjects aged less than 12 years who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects will be analyzed based on the randomized treatment assignment. The efficacy endpoints for cohort A1 will be analyzed using the seronegative mFAS-A1 unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B) - Cohort B

The seronegative modified full analysis set for cohort B (seronegative mFAS-B) includes all randomized subjects aged 12 years and older who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) and are asymptomatic at baseline.

Subjects will be analyzed based on the randomized treatment assignment. The primary and secondary endpoints for cohort B will be analyzed using the seronegative mFAS-B unless otherwise specified.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B1) - Cohort B1

The seronegative modified full analysis set for cohort B1 (seronegative mFAS-B1) includes all randomized subjects aged less than 12 years who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) and are asymptomatic at baseline. Subjects will be analyzed based on the randomized treatment assignment. The efficacy endpoints for cohort B1 will be analyzed using the seronegative mFAS-B1 unless otherwise specified.

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized subjects who received at least 1 dose or part of a dose of study drug. Subjects in the SAF will be analyzed based on the treatment received (as treated). In general, safety will be evaluated by study cohort: SAF-A (cohort A), SAF-B (cohort B), SAF-A1 (cohort A1), and SAF-B1 (cohort B1). However, injection site reactions will also be based on all cohorts combined.

11.3.3. Pharmacokinetic Analysis Set

The PK analysis population includes all subjects who received any study drug and who had at least 1 non-missing drug concentration measurement following study drug administration. Subjects will be analyzed based on actual treatment received.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set (AAS) includes all subjects who received study drug and had at least 1 non-missing ADA result after study drug administration. Subjects will be analyzed based on the actual treatment received.

11.3.5. Neutralizing Antibody Analysis Set

The NAb analysis set (NAS) includes all subjects who received any study drug and who are either negative in the ADA assay or positive for ADA with at least one non-missing result in the NAb assay after first dose of the study drug. Subjects who are ADA negative are set to negative in the NAb analysis set. Subjects will be analyzed according to the treatment actually received.

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of subjects reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Baseline is defined as the last assessment obtained before the first dose of study drug unless specified otherwise.

Statistical analyses will be conducted separately in each cohort. For the purpose of the study analysis, cohorts A, A1, B, and B1 are independent with separate type I error control for each cohort.

11.4.1. Subject Disposition

The following will be provided:

- The total number of screened subjects, defined as signed the ICF
- The total number of randomized subjects: received a randomization number
- The total number of subjects randomized but not receiving study treatment
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- A listing of subjects treated but not randomized, subjects randomized but not treated, and subjects randomized but not treated as randomized
- A listing of subjects prematurely discontinued from the study, along with reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all subjects combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

Cohort A

The cohort A primary efficacy endpoint described in Section 4.1.1 will be analyzed in the seronegative mFAS-A population (Section 11.3.1). All post-baseline efficacy assessments obtained up to last scheduled visit (day 29) in EAP will be included for the primary analysis.

In order to account for the correlation among subjects within a household and control the associated type 1 error inflation, a generalized linear model will be used to estimate the odds ratio between the treatment groups by using the GEE approach. This model estimates a single within-household correlation coefficient. The model will include the fixed category effects of treatment group (placebo versus REGN10933+REGN10987), region (US versus ex-US), and age (≥12 to <50, ≥50 years). The model will use a compound symmetry covariance matrix and estimate the odds ratio between the treatment groups and corresponding 95% CI and p-value.

If the GEE model fails to converge due to most households containing only a single study subject in seronegative mFAS-A or the percentage of households in cohort A with only a single study subject is 70% or more, then a logistic regression model will be used, with treatment, region, and age group as fixed effects. The threshold of 70% was based on simulations of within-household correlation which show the type I error rate is inflated and the power is decreased when the proportion of single-subject households is high. Additional details will be provided in the SAP. If the logistic regression model does not converge, an exact logistic regression will be used. The estimates of odds ratio, the corresponding 95% CI and p-value will be provided from logistic regression (or exact logistic regression) for comparison of REGN10933+REGN10987 against placebo group.

In cohort A, a subject will be considered having a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP if any of the post-baseline RT-qPCR results during EAP are positive with at least 1 symptom within 14 days of a positive RT-qPCR result.

Cohort B

The cohort B primary efficacy endpoint described in Section 4.2.1 will be analyzed in the seronegative mFAS-B population (Section 11.3.1). The same statistical methods as described for cohort A will be used to obtain the estimate of odds ratio and p-value for comparison between the treatment groups.

In cohort B, a subject will be considered having a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP if subjects have at least 1 symptom within 14 days of a positive RT-qPCR result at baseline or during the EAP.

Handling of Missing Central Lab SAR-CoV-2 RT-qPCR Data for Both Cohort A and Cohort B

Subjects with COVID-19 symptoms that are missing a central lab-determined RT-qPCR test during the EAP (eg, are too sick to go to the study site) but have a positive SARS-COV-2 test from a local lab (eg, in the hospital) will be considered as having a symptomatic infection if any of the symptoms occurred within 14 days of the positive SARS-COV-2 test(s).

The graphical display using Kaplan-Meier curve for the time to first symptom will also be provided.

11.4.3.1.1. Sensitivity Analyses

Robustness of the primary analyses results in cohort A and cohort B will be assessed through sensitivity analyses as follows:

Sensitivity analysis by excluding subjects who develop asymptomatic or symptomatic SARS-CoV-2 infection within 72 hours of the study drug administration

This analysis assesses for the sensitivity of the results to subjects who may have had undetected infections prior to dosing. That is, a subject had any onset of a positive RT-qPCR within 72 hours of the study drug administration will be excluded for this sensitivity analysis.

This sensitivity analysis will only be performed for cohort A primary endpoint.

Sensitivity analysis by excluding subjects from non-good clinical practice (GCP) Compliant Site(s)

To access the impact of sites that had non-GCP compliance issues on the primary efficacy points, the primary analyses will be performed by excluding non-GCP compliant site(s).

This sensitivity analysis will be performed for both cohort A and cohort B primary endpoints.

11.4.3.1.2. **Subgroup Analyses**

To assess the homogeneity of the treatment effect across various subgroups, the primary analysis model with GEE approach will be applied to each subgroup if applicable; otherwise, the logistic regression model will be used. Odds ratio between the treatment groups and corresponding 95% CI will be provided, as well as the within-household correlation coefficient from GEE approach, within each subgroup.

The subgroups of interest to be evaluated for cohort A primary endpoint include, but are not limited to:

- Stratification age group (years) (≥12 to <18, ≥18 to <50, ≥50) and the additional age group: ≥12 to <18, ≥18 years
- Sex
- Race
- Ethnicity
- BMI (<30, ≥30)
- Number of study subjects in cohort B within a household (0, ≥1) (cohort A only)
- Total household size including the household member(s) not participating this study (2, and >2)
- Region (US, ex-US)

Additional subgroup analyses will be defined in the SAP.

11.4.3.2. Key Secondary Efficacy Analyses

For cohort A, the key binary endpoint of the proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP, the same statistical method used in the primary analysis will be applied. If a subject's overall infection status during the EAP cannot be determined due to missing RT-qPCR results, the following rules will be applied to impute the missing RT-qPCR data.

1. For subjects satisfying the criteria specified in the handling of missing central lab SARS-CoV-2 RT-qPCR data of the analysis of primary efficacy variables, the corresponding visit(s) will be considered as having a positive RT-qPCR test.
2. After the first step above, each planned visit with missing RT-qPCR data will be imputed 100 times to generate 100 complete datasets based on the predicted probability using the fully conditional specification (FCS) (Van Buuren, 2006) through the logistic regression. The logistic regression model includes the fixed effect factors of treatment group, region, age group, and RT-qPCR testing status at other analysis visits during the EAP. This imputation will repeat by iterating for each analysis visit with missing RT-qPCR testing status. Full details on details on the use of FCS from the SAS MI procedure will be provided in the SAP.

For the key binary endpoint of the proportion of subjects with viral load >4 (log10 copies/mL), if NP swab viral load data is missing for a visit, it will not be imputed regardless of symptoms. Only non-missing available NP swab viral load data will be used for the analysis of this endpoint. Only subjects with at least one post-baseline viral load (log10 copies/mL) data in NP swab samples will be included in the analysis.

For cohort A the key binary endpoint regarding the index case linkage to R10933-10987-COV-2067, the Fisher's exact test will be used.

For continuous key secondary endpoints in cohort A and cohort B (eg, number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples and number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) during the EAP, etc), visits with missing viral load regardless of symptoms and visits with missing RT-qPCR that do not have any broad-term symptoms within 14 days will not be considered as meeting these endpoint criteria, respectively. These endpoints will be analyzed by the non-parametric method, a stratified Wilcoxon rank sum test (Van Elteren Test) with the region and age group. Descriptive statistics will be provided for number (%) of subjects with each interval of duration in weeks (ie, 0 week, > 0 to ≤ 1 week, > 1 to ≤2 weeks, etc) within each treatment group. The total weeks of infection and normalized duration (eg, average duration infection per 1000 subjects) per treatment group will also be reported.

11.4.3.3. Other Secondary Efficacy Analyses

Other secondary efficacy endpoints will be analyzed by type of endpoint for all cohorts. The analysis methods for key secondary efficacy endpoints in both cohort A and cohort B will also be applied to efficacy endpoints for exploratory endpoints in both cohort A and cohort B if appropriate. The primary approach to the data will be through descriptive statistics. For the comprehensive evaluation of efficacy, nominal p-values may be reported. Raw data descriptive statistics will also be presented.

Other secondary efficacy endpoints and exploratory endpoints for cohort A1 and cohort B1 will also be analyzed by type of endpoint. If the sample size is sufficient, continuous variables will be summarized by the descriptive statistics (eg, n, mean, SD, Q1, median, Q3, minimum and maximum, etc.). Binary variables will be summarized using the number and percentage of subjects in each treatment group. No statistical hypothesis testing will be performed for cohort A1 and cohort B1. This approach may also be applied to adolescent subjects.

Binary Endpoints

The binary endpoints in cohort A and cohort B will be analyzed applying the same approach used for the primary efficacy endpoints. The details will be provided in the SAP.

Continuous Endpoints

The secondary and exploratory continuous efficacy endpoints such as TWA, AUC, and maximum viral load (log10 copies/mL) will be analyzed using the ANOVA including treatment group, region, and age group as fixed effects or using the ANCOVA if adjusting by the relevant baseline values as covariate and treatment-by-covariate interaction are needed. For other endpoints with non-normal/skewed distribution, the Van Elteren test used in the key secondary endpoints will be applied.

11.4.4. Control of Multiplicity

The overall type I error will be controlled in each of seronegative mFAS-A and seronegative mFAS-B independently at 2-sided 5% significance level.

Seronegative mFAS-A Subjects

The overall type I error will be controlled for the primary hypothesis in cohort A based on a 2-sided test at an alpha level of 0.05 as follows:

H0: There is no treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during EAP.

H1: There is a treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP

If the primary efficacy endpoint in cohort A is statistically significant, the alpha level of 0.05 will be released for the key secondary endpoints in cohort A. The hierarchical testing sequence for key secondary efficacy endpoints is presented in Table 10.

Table 10: Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-A

Key Secondary Efficacy Endpoints
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP
Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) during the EAP
Number of weeks of high-viral load >4 (log10 copies/mL) in NP swab samples during the EAP
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 versus placebo in R1033-10987-COV-2067)

Seronegative mFAS-B Subjects

The overall type I error will be controlled for the primary hypothesis in cohort B based on a 2-sided test at an alpha level of 0.05 as follows.

H0: There is no treatment difference between REGN10933+REGN10987 and placebo in proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

H1: There is a treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

If statistical significance is established for the primary efficacy endpoint in cohort B, a hierarchical testing procedure will be applied to the key secondary endpoints in cohort B at a 2-sided 0.05 significance level. The order of testing sequence for key secondary endpoints is presented in Table 11.

Table 11: Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-B

Key Secondary Efficacy Variables
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
Number of weeks of high viral load (log10 copies/mL) >4 in NP swab samples during the EAP

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent EAP is defined as the day from first dose of study drug to 28 days after the last dose of study drug.
- The treatment-emergent follow-up period is defined from the day after the end of the treatment-emergent EAP to the end of the Follow-up Period (ie, last study visit).

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition.

Treatment-emergent adverse events (TEAEs) will be summarized for each of the following periods: treatment-emergent EAP, treatment-emergent follow-up period, and combined across the treatment-emergent EAP and treatment-emergent follow-up periods. Adverse events that occur prior to treatment will be listed.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®), version 23.0 or greater. Coding will be to lowest level terms. The preferred term (PT), and the primary system organ class (SOC) will be listed.

The number and percentage of subjects with TEAEs will be summarized by treatment group. Summaries will include:

- Overview of TEAEs, ie, overall number (%) of subjects with any TEAE, Serious TEAE, TEAE leading to death, or TEAE leading to study drug withdrawn
- TEAEs by primary SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT
- Treatment-emergent SAEs by primary SOC and PT
- Treatment-emergent AESIs by primary SOC and PT
- Treatment-emergent AEs leading to study drug withdrawn by primary SOC and PT

Similar summaries as described above will also be provided for adult, adolescent and pediatric subjects (<12 years), respectively. Deaths and other SAEs will be listed and summarized by treatment group.

In addition, the number and percentage of subjects with symptomatic SARS-CoV-2 infections, and the severity of the infection will be summarized by treatment group. SARS-CoV-2 infection will be summarized for each of the following periods: EAP and Follow-up period.

11.4.5.2. Other Safety (Vital Signs and Laboratory Tests)

Definitions

The following definitions will be applied to laboratory parameters and vital signs:

- The potentially clinically significant value (PCSV) criteria are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs. The PCSV criteria will be provided in the SAP.
- PCSV criteria will determine which subjects had at least 1 PCSV during the respective TEAE periods, taking into account all evaluations performed during the respective TEAE periods, including unscheduled or repeated evaluations. The number of all such subjects will be the numerator for the PCSV percentage.

Analysis

The incidence of PCSVs at any time during the TEAE period will be summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal/missing
- Abnormal according to PCSV criterion or criteria

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided for subjects meeting PCSV criteria and subjects with any positive RT-qPCR test results, respectively.

11.4.5.3. Treatment Exposure

The duration of study treatment exposure will be defined as 28 days after the last dose for a subject in SAF. The follow-up period is defined as 8 months after the dose administration.

11.4.5.4. Treatment Compliance

Subject treatment compliance is not applicable for this study, since the study drug is administered once at the site and will be the same as treatment exposure.

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Dense Samples for Drug Concentration

The PK parameters to be determined for REGN10933 and REGN10987 may include, but are not limited to:

C_{max}, t_{ax}, t_{last}, C_{last}, AUC_{inf}, $t_{1/2}$, C_{28} (concentration in serum 28 days after dosing)

Selected PK parameters will be summarized by descriptive statistics for each cohort. All parameters will be summarized (mean, SD, %CV, range, median, and number of samples).

Sparse Samples for Drug Concentrations

The concentrations of REGN10933 and REGN109877 in serum over time will be summarized by descriptive statistics for each cohort.

No formal statistical hypothesis testing will be performed.

11.4.7. Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

At a minimum, exposure-response analyses will be performed for selected virologic endpoints. Additional exposure response analyses will be performed for safety endpoints and/or biomarkers, as appropriate.

11.4.8. Analysis of Immunogenicity Data

Immunogenicity will be characterized by ADA and NAb responses and titers observed in subjects in the ADA and NAb analysis sets. The ADA response categories and titer categories are defined as follows:

ADA response categories:

- ADA Negative, defined as ADA negative response in the ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, or a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when baseline results are negative or missing.
- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer categories (Maximum titer values)

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive subjects by treatment groups and ADA titer categories
- Number (n) and percent (%) of treatment-boosted ADA positive subjects by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for subjects with pre-existing, treatment-emergent, and treatment-boosted ADA response.

The absolute occurrence (n) and percent of subjects (%) with NAb status in the NAb analysis set will be provided by treatment groups.

11.4.9. Timing of Statistical Analysis

There are multiple steps of analyses planned for this study.

- An administrative assessment based on approximately first 554 randomized cohort A subjects has been conducted. No formal statistical hypothesis testing was performed. (Section 11.2). The individuals who can access the subject treatment information will be described in the communication plan. These 554 subjects will not be included in the first-step or second-step efficacy analyses described below.

- The first step analysis (primary analysis): The database lock will occur when all cohort A and cohort B subjects complete the EAP. The data during the EAP has been collected and validated for all subjects who were randomized by 28 Jan 2021. Subjects who are randomized after 28 Jan 2021 (approximately 269 subjects) will not be included in this first-step analysis. The individual treatment codes will be unblinded and final analyses of the primary and some secondary efficacy endpoints of cohort A and cohort B will be conducted.

  Note: The results of primary and some secondary efficacy endpoints in the first step analysis maybe used for a submission dossier to health authorities.

- The second step analysis (final analysis): The database lock will occur after the last subject completes the study. All treated subjects, including 554 subjects in the administrative assessment, subjects in the first step analysis, and those subjects (approximately 269 subjects) who were randomized after 28 Jan 2021, will be included in the safety analysis. The second-step analysis for efficacy will include all subjects except those subjects who were included in the administrative assessment.

11.5. Interim Analysis

No interim analysis will be conducted for this study.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC)

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk based approach to study monitoring and oversight, aligned with risk based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of subjects are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate subject records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every subject enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each subject, the investigator must provide an electronic signature. A copy of each subject CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor’s participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of subject final eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

Adult Subjects

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the subject in language that he/she can understand. The ICF should be signed and dated by the subject and by the investigator or authorized designee who reviewed the ICF with the subject.

- Subjects who can write but cannot read will have the ICF read to them before signing and dating the ICF.

- Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study subjects must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the subject's study record and a copy must be given to the subject.

Pediatric Subjects: Adolescent and Children (<12 years)

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each subject and his/her parent(s) or legal guardian(s) prior to the subject's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the subject and the parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the subject's parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF.

Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The subject may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Subjects who can write but cannot read will have the assent form read to them before writing their name on the form.
- Subjects who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject's parent(s) or legal guardian(s).

13.3. Subjects Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects should be identified by a subject identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence. Government agencies such as Health and Human Services, other health authorities, IRBs/ ECs, and staff/contractors may review these records, as appropriate.

The subject 's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the subjects (eg, advertising) before any subject may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subject, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any subject within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of subjects required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the subjects' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: *A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2* and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

______________________________ ____________________

(Signature of Investigator) (Date)

____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-CoV-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2

Protocol Number: R10933-10987-COV-2069

Protocol Version: R10933-10987-COV-2069 Amendment 6

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00142963 v1.0

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Signature Page for VV-RIM-00142963 v1.0 Approved

AMENDMENT HISTORY

Amendment 6

The primary purpose of this amendment is to revise and add objectives and endpoints, as well as to define the statistical testing hierarchy for the primary and key secondary endpoints.

Description of Change	Brief Rationale	Section(s) Changed
Objectives, Endpoints, and Planned Statistical Analysis		
The following modifications were made to the planned statistical analysis: • Revised the primary objective and endpoint for cohort A	The revision of the primary objective and endpoint for cohort A is informed by the administrative assessment of 409 cohort A seronegative subjects, where there was a 100% reduction in symptomatic events (broad-term) in the REGN10933+REGN10987 treated subjects as compared to the placebo treated subjects with 8/223 (3.6%) placebo treated subjects developing symptomatic infection versus 0/186 (0%) REGN10933+REGN10987 treated subjects; OR 0.00 (0.00, 0.69) p<0.01. The single primary objective is now to evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR	Clinical Study Protocol Synopsis: Objectives, Endpoints, Statistical Plan Section 2 Study Objectives Section 2.1.1.1 Cohort A Primary Efficacy Objective Section 4 Endpoints Section 4.1.1 Cohort A Primary Endpoints Section 6.1.6 Description of Study Cohorts Section 9.2.2.2 COVID-19 Symptomology (Strict Terms, Broad Terms, and CDC Definition)
• Added a primary objective and endpoint for cohort B	Because cohort B is a separate population from cohort A, where cohort B subjects are infected at baseline (SARS-CoV-2 RT-qPCR positive), a new primary objective and endpoint was added to evaluate whether REGN10933+REGN10987 may be efficacious as preemptive therapy to prevent symptoms in those who are already infected, therefore the objective is to evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing COVID-19 symptoms (broad-term) in asymptomatic subjects that are SARS-CoV-2 RT-qPCR positive and seronegative at baseline	Section 2.2 Cohort B and Cohort B1: SARS-CoV-2 RT-qPCR Positive at Baseline Section 2.2.1 Cohort B Primary Efficacy Objective Section 2.2.2 Cohort B and Cohort B1 Primary Safety Objective Section 4.2.1 Cohort B Primary Efficacy Endpoint
Defined key secondary endpoints for all cohorts	The revision of the key secondary objectives and endpoints is informed by the administrative assessment of 409 cohort A seronegative subjects, such that revised key secondary endpoints now include the evaluation of REGN10933+REGN10987 as compared to placebo to reduce high viral load, defined as viral load >4 ($\log_{10}$ copies/mL), duration of symptomatic infection, duration of high viral load infection, duration of any infection, development of infection (regardless of symptoms), all during the 28 day efficacy	Section 4.1.2 Cohort A Key Secondary Endpoints Section 4.2.2 Cohort B Key Secondary Endpoints

	assessment period. An additional key secondary endpoint links the Regeneron R10933-10987-COV-2067 outpatient treatment study with the R10933-10987-COV-2069 prevention study, where households who enrolled symptomatic infected household members into 2067 and their asymptomatic uninfected members into 2069. These data may inform whether treatment of symptomatic infected household members with REGN10933+REGN10987 may prevent infection in uninfected household members.	
• Revised the secondary and exploratory objectives and endpoints for all cohorts	Objectives and endpoints that were determined not to be key are listed as other secondary and exploratory.	Section 2.1.3 Cohort A and Cohort A1 Secondary Objectives Section 2.1.4 Cohort A and Cohort A1 Exploratory Objectives Section 4.1.3 Cohort A and Cohort A1 Other Secondary Endpoints Section 4.1.4 Cohort A and Cohort A1 Exploratory Endpoints Section 2.2.3 Cohort B and Cohort B1 Secondary Objectives Section 2.2.4 Cohort B and Cohort B1 Exploratory Objectives Section 4.2.3 Cohort B and Cohort B1 Other Secondary Efficacy Endpoints Section 4.2.4 Cohort B and Cohort B1 Exploratory Endpoints
• Updated the statistical hypotheses and the planned analyses for efficacy and safety	Statistical hypothesis and planned analyses were updated in accordance with the revised primary(s) and key secondary objectives and endpoints	Section 11.1 Statistical Hypothesis Section 11.4 Statistical Methods Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.1.1. Sensitivity Analyses Section 11.4.3.1.2. Subgroup Analyses Section 11.4.3.2. Key Secondary Efficacy Analyses Section 11.4.3.3. Other Secondary Efficacy Analyses Section 11.4.1 Subject Disposition Section 11.4.5.1. Adverse Events

• The scope of analyses for first-step and second-step analyses were specified. • The data-cutoff for the first step analysis was specified	The rationale for scope of analyses and the first-step analysis data cut off are based on the results of the administrative assessment and the sample size justification.	Section 11.4.9. Timing of Statistical Analysis
• Defined the statistical testing hierarchy for the primary endpoint and key secondary endpoints for cohort A and cohort B	The statistical testing hierarchy was determined by considering which endpoints would be most relevant and important to understand the efficacy of REGN10933+REGN10987 to prevent symptomatic infection and transmission potential, including the prevention of infections with high viral loads, longer duration of high viral loads, and whether REGN10933+REGN10987 can be considered for treatment of the symptomatic infected household member to prevent infection of the uninfected household member.	Section 11.4.4. Control of Multiplicity Table 10 Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-A Table 11 Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-B
• Updated the sample size justification	Based on the decision not to conduct any interim analysis, the full alpha will be used for the first-step analysis.	Section 11.2 Justification of Sample Size Table 9 Simulated Power for Household Design (1248 Subjects over 430 Households Section 11.2.1 Cohort A: Adult and Adolescent Subjects (≥12 years) Who Are SARS-CoV-2 RT-qPCR Negative at Baseline Section 11.2.2 Cohort B: Adult and Adolescent Subjects (≥12 years) Who Are SARS-CoV-2 RT-qPCR Positive at Baseline
• Updated the analysis set definitions	The definitions were revised to specify that only seronegative subjects are eligible for the efficacy analysis sets.	Section 11.3.1 Efficacy Analysis Sets Section 11.3.2 Safety Analysis Set Section 11.3.4 Immunogenicity Analysis Set Section 11.3.5 Neutralizing Antibody Analysis Set
• Added statement that no interim analysis will be conducted for this study	No interim analyses will be conducted for this study.	Section 8.5 Blinding Section 11.5 Interim Analysis
• Updated the variable definition for SARS-CoV-2 infection	The definition for positive and negative infection results was revised for consistency with the statistical analyses specified.	Section 5.2 Efficacy Variables
Clinical Rationales for the Changes to Objectives and Endpoints		
• Provided the rationales for the changes to the objectives and endpoints	The rationales for the primary and secondary objectives and endpoints were revised based on the results of the administrative assessment .	Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 3.2.5 Primary Objective

		Section 3.2.6 Secondary Objectives
Study Design		
• Added collection of external SARS-CoV-2 test results for subjects with COVID-19 symptoms	Collection of local SARS-CoV-2 test results will support confirmation of infection in subjects with COVID-19 symptoms	Section 6.1.4 Efficacy Assessment Period Section 6.1.5 Follow-up Period Section 8.8 Concomitant Medications and Procedures Section 9.1.1 Schedule of Events Table 3 (Cohorts A and B [Adult /Adolescent Subjects], RT qPCR-Negative and Positive) Footnotes), footnote #9 Section 11.4.3.1 Primary Efficacy Analysis
Other changes		
• Updated confidentiality statement	Revised per current corporate version	Title Page
• Minor editorial updates -changed verb tense -fixed numbered list formatting	Corrected minor issues.	Throughout the document

Amendment 5

The primary purpose of this amendment is to describe the verification of the sample size assumptions used to design the study.

Description of Change	Brief Rationale	Section(s) Changed
• Added an administrative assessment for assumption verification and sample size estimation for the study • Sample size increased to 3500 subjects to ensure that the formal analysis of the phase 3 study has an adequate sample size.	The initial sample size assumptions used for the study design were based on COVID-19 household contact infection rates observed in the literature available during study planning. Currently, the range of reported infection rates, including onset of infection and symptomatic infection, is more variable in the literature than originally understood. Some early study data will be used, therefore, to verify the assumptions and estimated sample size by assessing infection rates in the population in this study.	Clinical Study Protocol Synopsis: Study Design, Population, Statistical Plan Section 3.2.2 Subject Population Section 6.1 Study Description and Duration Section 7.1 Number of Subject Planned Section 11.2 Justification of Sample Size Section 11.2.1 Cohort A- SARS-CoV-2 RT-qPCR Negative Section 8.5 Blinding Section 11.3.1 Full Analysis Sets Section 11.4.9 Timing of Statistical Analysis
• Consolidated the dose information into a single section of the protocol	The dose information is presented in one section.	Section 8.1 Investigational and Reference Treatments Section 8.4 Method of Treatment Assignment
• Added guidance related to the use of an EUA approved COVID-19 vaccine by subjects in the study	Specified that an EUA approved COVID-19 vaccine is prohibited during the EAP and permitted in the Follow-up period. The unblinding performed for the purpose of COVID-19 vaccine decision making does not need to be discussed with the medical director.	Section 8.6 Emergency Unblinding Section 8.9 Prohibited Medications Section 8.10 Permitted Medications
• Added collection of information for the household members related to an EUA approved monoclonal antibody treatment for COVID-19 or participation in the R10933-10987-COV-2067 study	Collection of this information is needed to understand the COVID-19 transmission in the household setting.	Section 9.1.1 Schedule of Events Table 3 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes, #16 Section 9.1.3 f Schedule of Events Table 5 Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Footnotes, # 15 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit
• Updated the title for medical/study directors	The medical/study director title were updated	Title page

Amendment 4

The primary purposes of this amendment are 1) to change from 2 primary endpoints to 1 primary endpoint, 2) to increase the sample size, 3) to allow for the inclusion of pediatric subjects aged <12 years, 4) to allow for the inclusion of women who are pregnant or breastfeeding, and 5) to add an exploratory objective and endpoint to assess whether the treatment of index cases with REGN10933+REGN10987 in the R10933-10987-COV-2067 study has an impact on rates of infectivity in household contacts in this study. The endpoint and sample size changes are based on blinded review of the data with regard to SARS-CoV-2 infection events and baseline seropositivity prevalence in cohort A. The inclusion of pediatric subjects younger than 12 years and pregnant or breastfeeding women is considered relevant to the populations at risk for infection with SARS-CoV-2.

Description of Change	**Brief Rationale**	**Section(s) Changed**
• Study now has 1 primary efficacy endpoint: proportion of SARS-CoV-2 infection during the efficacy assessment period (EAP). The proportion of "strict-term" symptomatic SARS-CoV-2 infection during the EAP has been moved to a secondary endpoint.	A blinded analysis of approximately 25% of enrolled subjects was performed, demonstrating that lower than expected symptomatic infection events were observed in Cohort A: adult and adolescent Subjects (≥12 years) who are SARS-CoV-2 RT-qPCR Negative at Baseline. If 2 primary endpoints were to be retained, the study is considered infeasible as the sample size would need to increase several fold to have enough symptomatic events in cohort A to be powered sufficiently. The single primary endpoint of the prevention of laboratory confirmed SARS-CoV-2 infection is considered highly clinically important because infection is the necessary antecedent event for illness.	Clinical Study Protocol Synopsis: Primary Endpoints, Secondary Endpoints, Statistical Plan Section 3.2.5 Primary Objectives Section 3.2.6 Secondary Objectives Section 4.1.1 Cohort A Primary Endpoints Section 4.1.2 Cohort A and Cohort A1 Secondary Endpoints Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.4.1 Cohort A
• Increased the sample size for the study	A blinded analysis of approximately 25% of enrolled subjects was performed, demonstrating a higher than expected seropositivity rate at baseline in Cohort A. The sample size of cohort A is therefore being revised upwards to account for this seropositivity rate because only seronegative individuals are included in the primary analysis population.	Section 7.1 Number of Subjects Planned Section 11.2 Justification of Sample Size Section 11.2.1 Cohort A- SARS-CoV-2 RT-qPCR Negative Section 11.2.2 Cohort B - SARS-CoV-2 RT-qPCR Positive
• Pediatric subjects aged <12 years are added to the study. • Added description of the informed consent for the parent/guardian and assent for pediatric subjects	Pediatric subjects <12 years of age are added to the study because they are a population at risk of SARS-COV-2 infection in a household and may contribute to the infection of others in the household. Pregnant women who are household contacts of an index case are at risk of SARS-CoV-2 infection and are at higher	Clinical Study Protocol Synopsis: Objectives, Study Design, Sample Size, Target Population, Treatments, Primary Endpoints, Secondary Endpoints, Procedures and Assessments, Statistical Plan Section 1.2 Populations at Increased Risk of SARS-CoV-2 Infection Among Household Contacts of a Person Infected with SARS-CoV-2

• Pregnant women and breastfeeding women are added to the study. • The requirement for contraception use by women of childbearing potential (WOCBP) was removed • The requirement for contraception use by men enrolled in the study was removed. • The stratification for pediatric subjects in randomization will take weight group into account (ie, ≥20 kg, ≥10 kg to <20 kg, and <10 kg).	risk of severe COVID-19 than non-pregnant women. Inclusion of pediatric subjects, pregnant women, and breastfeeding women is supported by ongoing blinded review of the safety profile in adult and adolescent subjects, which is demonstrating that REGN10933+REGN10987 treatment is sufficiently well-tolerated. In addition, there is no human fetal tissue cross-reactivity of REGN10933 and REGN10987 to suggest a risk to the fetus. The safety profile in pediatric subjects less than 12 years and pregnant and breastfeeding women is expected to be similar to that observed in adults and adolescents. Because pregnant women are allowed in the study, contraception for women of childbearing potential (WOCBP) is no longer required as an exclusion criterion. However, WOCBP will undergo pregnancy testing prior to dosing and at the end of study. Women who are pregnant or who become pregnant during the study will be followed for the outcome of their pregnancy. The inclusion of pregnant women who are identified at study entry as well as women who become pregnant during the study will provide important safety and efficacy data in this population at increased risk of severe COVID-19. Because pregnant women are allowed in the study, contraception for men enrolled in the study is no longer required as an exclusion criterion. Information regarding pregnancies occurring in the female partners of male study subjects will not be solicited as the risk of exposure is negligible in this scenario The stratification is to ensure relative balance in treatment allocation among different pediatric weight groups for PK analysis.	Section 1.5 A Randomized, Placebo-Controlled Study of Anti- Spike Protein Monoclonal Antibodies as Post-Exposure Prophylaxis and Pre-emptive Therapy in Household Contacts Section 3.2.1 Study Design Section 3.2.2 Subject Population Section 3.2.4 Sentinel Safety Group and Subsequent Safety Reviews Section 3.3 Risk-Benefit Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 6.1.2 Pediatric Subjects (<12 years) Section 6.1.3 Screening/Baseline Section 7.1 Number of Subjects Planned Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, criterion #1 Section 7.2.2 Exclusion Criteria, #14, #15, #16 Section 8.6 Emergency Unblinding Section 13.2 Informed Consent
• Specified doses for subjects <12 years of age using weight-tiered dosing groups	Based on population pharmacokinetics modeling and simulation, lower doses were selected for children using a weight-tiered approach in order to achieve approximately	Section 3.2.7 Rationale for Dose Selection Figure 1 Study Flow Diagram

	similar exposures as those observed in adults. Weight is the primary variable influencing drug exposure.	Section 8.1 Investigational and Reference Treatments Section 8.4 Method of Treatment Assignment Section 9.2.4 Drug Concentration and Measurements Table 6 Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.1.4 Schedule of Events Table 6 Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing
• Subjects <12 years of age will be divided into 2 independent study cohorts, cohort A1 (SARS-CoV-2 RT-PCR negative at baseline) or cohort B1 (SARS-CoV-2 RT-PCR positive at baseline) using the same parameters used to define cohort A and B for the adult and adolescent subjects. • Study objectives and endpoints were specified for cohort A1 and cohort B1 • Cohort A1 and cohort B1 will be analyzed separately from the adult and adolescent subjects.	The pediatric subjects <12 years are proposed to be analyzed separately from the adults and adolescents because 1) drug concentrations and exposures need to be evaluated and may change during the study, 2) nasopharyngeal (NP) sampling for RT-qPCR is not identical to that used for adult and adolescent subjects, 3) subjects <12 years may have milder disease, 4) COVID-19 signs and symptoms/AE reporting may be different in subjects <12 years	Clinical Study Protocol Synopsis: Objectives, Sample Size, Target Population, Treatments, Primary Endpoints, Secondary Endpoints, Statistical Plan Section 2 Study Objectives Section 2.1 Cohort A: SARS-CoV-2 RT qPCR Negative at Baseline Section 2.1.2 Cohort A and Cohort A1 Primary Safety Objective Section 2.1.3 Cohort A and Cohort A1 Secondary Objectives Section 2.1.4 Additional Cohort A1 Secondary Efficacy Objective Section 2.1.5 Cohort A and Cohort A1 Exploratory Objectives Section 2.2 Cohort B and Cohort B1: SARS-CoV-2 RT qPCR Positive at Baseline Section 2.2.1 Cohort B and Cohort B1 Secondary Objectives Section 2.2.2 Cohort B and Cohort B1 Exploratory Objectives Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 4.1 Cohort A and Cohort A1: SARS-CoV-2 RT-qPCR Negative at Baseline Section 4.1.1 Cohort A Primary Endpoints

		Section 4.1.2 Cohort A and Cohort A1 Secondary Endpoints Section 4.1.3 Cohort A and Cohort A1 Exploratory Endpoints Section 4.2 Cohort B: SARS-CoV-2 RT-qPCR Positive at Baseline Section 4.2.1 Cohort B and Cohort B1 Secondary Efficacy Endpoints Section 4.2.2 Cohort B and Cohort B1 Exploratory Endpoints Section 6.1.6 Description of Study Cohorts Section 11.3.1 Full Analysis Sets Section 11.4.3.2 Secondary Efficacy Analyses Section 11.4.5.1 Adverse Events
• Specified assessments for cohort A1 and cohort B1 (subjects <12 years of age)	The assessments were modified for pediatric subjects younger than 12 years to minimize blood draws and procedures.	Clinical Study Protocol Synopsis: Procedures and Assessments Table 3 Schedule of Events (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 2 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes #2, #4, #6, #12, #18, #19, #20 Table 4 Schedule of Events: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.1.2 Schedule of Events Table 3: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentrations, Immunogenicity, and Laboratory Testing Table 5 Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Section 9.1.3 Schedule of Events Table 4 Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Footnotes Table 6 Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing

		Section 9.1.4 Schedule of Events Table 5: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.2.2.1 Nasopharyngeal Swab SARS-CoV-2 RT-qPCR Test (Central Lab) Section 9.2.2.2 COVID-19 Symptomology (Strict Terms, Broad Terms, and CDC Definition) Section 9.2.2.3 Assessment of Medically Attended Visits Section 9.2.2.4 Absenteeism Assessment Section 9.2.3.1Targeted Physical Examination and Vital Signs Section 9.2.3.2 Laboratory Testing Section 9.2.6 Exploratory Pharmacodynamic/Biomarker Procedures [redacted] Section 10.1.3 Events that Require Expedited Reporting to Sponsor
• Added exploratory objective to assess the impact of the treatment of index cases receiving REGN10933+REGN10987 in study R10933-10987-COV-2067 on rates of infectivity in household contacts	Included to study the infection dynamics within a household and assess if the treatment of the index case with REGN10933+REGN10987 in study R10933-10987-COV-2067 affects secondary infection rates in study R10933-10987-COV-2069.	Section 2.1.5Cohort A and Cohort A1 Exploratory Objectives Section 4.1.3Cohort A and Cohort A1 Exploratory Endpoints Section 9.1.1Schedule of Events Table 2 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnote #16
• Added a secondary objective and an endpoint based on the CDC definition of COVID-19 symptoms	The use of the CDC definition for a secondary objective and an endpoint support comparability of results across clinical studies in the field.	Clinical Study Protocol Synopsis: Objectives, Endpoints, Secondary Endpoints, Procedures and Assessments, Statistical Plan Section 2.1.3 Cohort A and Cohort A1 Secondary Objectives Section 2.2.1 Cohort B and Cohort B1 Secondary Objectives Section 3.2.6 Secondary Objectives Section 4.1.2 Cohort A and Cohort A1 Secondary Endpoints Section 4.1.3 Cohort A and Cohort A1 Exploratory Endpoints Section 4.2.1 Cohort B and Cohort B1 Secondary Efficacy Endpoints

		Section 4.2.2 Cohort B and Cohort B1 Exploratory Endpoints Section 5.2 Efficacy Variables Section 9.2.2.2 COVID-19 Symptomology (Strict Terms, Broad Terms, and CDC Definition) Table 7 Strict-Terms ,and Broad-Terms, and CDC Definition COVID-19 Signs and Symptoms
• Changed the definition of the index case such that the index case must be the first household member known to be infected with SARS-CoV-2	Adding the requirement that the index case be the first known infected household member in the house may increase the number of household members who have not yet been exposed to SARS-CoV-2 and may therefore still be susceptible to infection.	Clinical Study Protocol Synopsis: Study Design, Target Population Section 2 Study Objectives Section 3.2.1 Study Design Section 3.2.2 Subject Population Section 6.1 Study Description and Duration Section 6.1.6 Description of Study Cohorts Section 7.2 Study Population Section 7.2.2 Exclusion Criteria, #2
• Revised the description of the screening and baseline visit to allow a remote visit to occur on the day prior to randomization and study drug administration to sign the informed consent form and collect medical history and concomitant medication use.	Provide flexibility for subjects to complete the screening remotely so that in-person screening may be abbreviated due to COVID-19 considerations	Section 6.1 Study Description and Duration Section 9.1.1 Schedule of Events Table 2 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes #1
• Added assessment of neutralizing antibodies, if feasible	Provide information about the assessment of NAbs in the study	Clinical Study Protocol Synopsis: Secondary Endpoints Section 3.2.1 Study Design Section 4.1.2 Cohort A and Cohort A1 Secondary Endpoints Section 4.2.2 Cohort B and Cohort B1 Exploratory Endpoints Section 5.5 Immunogenicity Variables Section 9.1.2 Schedule of Events Table 3: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentrations, Immunogenicity, and Laboratory Testing Section 9.1.4 Schedule of Events Table 5: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.2.5 Immunogenicity Measurements and Samples

		Section 11.3.4 Immunogenicity Analysis Sets Section 11.4.8 Analysis of Immunogenicity Data
• Added a description of current approved treatment and therapies for COVID-19	Provide information about current treatments and therapies for COVID-19	Section 1.5 A Randomized, Placebo-Controlled Study of Anti- Spike Protein Monoclonal Antibodies as Post-Exposure Prophylaxis and Pre-emptive Therapy in Household Contacts
• Clarified the exclusion of drugs used to treat COVID-19	Specified that prohibited drugs (eg, hydroxychloroquine) can be used to treat a non-COVID-19 disease (eg, autoimmune disease).	Section 7.2.2 Exclusion Criteria, #2, #12 Section 8.9 Prohibited Medications
• Minor editorial updates -added abbreviations -changed verb tense - added and deleted references	Updated the abbreviation and reference lists.	Throughout the document

Amendment 3

The primary purpose of this amendment is to include adolescent subjects aged 12 years to less than 18 years in the study. The inclusion of adolescent subjects is considered relevant to the populations at risk for infection with SARS-CoV-2.

Description of Change	**Brief Rationale**	**Section(s) Changed**
• Adolescent subjects aged 12 years to less than 18 years are added to the study • Provided a rationale for dose selection for adolescent subjects (≥40 kg) • Revised the description of women of childbearing potential (WOCBP) to include 'girls at or beyond menarche (≥12 to <18 years of age)' • Added description of the informed consent process	Adolescent subjects ≥12 to <18 years of age (weight ≥40 kg) are added to the study because they are a population at risk of SARS-CoV-2 infection in a household. Inclusion of adolescent subjects is supported by ongoing blinded review of the safety profile, which is demonstrating that REGN10933+REGN10987 treatment is well-tolerated in more than 1000 adult subjects who have received drug. Defined the age range for adolescent female subjects to be considered WOCBP.	Clinical Study Protocol Synopsis: Study Design, Population, Treatments, Procedures and Assessments, Statistical Plan Section 1.2 Populations at Increased Risk of SARS-CoV-2 Infection Among Household Contacts of a Person Infected with SARS-CoV-2 Section 2 Study Objectives Section 3.2.1 Study Design Section 3.2.2 Subject Population Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 3.2.4 Sentinel Safety Group and Subsequent Safety Reviews Section 3.2.5 Primary Objectives Section 3.2.6 Rationale for Dose Selection Section 3.3 Risk-Benefit Section 6.1 Study Description and Duration

for adolescent subjects and their parent/guardian • The stratification for age group in randomization will take adolescents into account (ie, ≥12 to <18, ≥18 to <50, ≥50). • Specify the sample size re-estimation will be conducted periodically, starting when approximately 25% of subjects in cohort A have completed the efficacy assessment period (EAP). • Summaries of treatment-emergent adverse events (TEAEs) for adolescent subjects will also be provided.	Provided instruction for documenting consent of the adolescent subject and their parent/guardian The stratification is to ensure relative balance in treatment allocation in adolescents. The rate of symptomatic SARS-CoV-2 infections among adolescent subjects may differ from adults. Since adolescent subjects are being added after the start of the study, greater flexibility in the timing of the sample size re-estimations is needed to ensure that the attack rate can be estimated for adolescent subjects. To evaluate the safety data among adolescent subjects.	Section 6.1.1 Sentinel Subjects and Staggered Enrollment/Dosing Section 6.1.2 Screening/Baseline Section 6.1.3 Efficacy Assessment Period Section 6.1.4 Follow-up Period Section 6.1.5 . Description of Study Cohorts Section 6.3.2 Safety Review Committee for REGN 2069/CoVPN3502 Section 7.1 Number of Subjects Planned Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, criterion #1 Section 7.2.2 Exclusion Criteria, #16 Section 7.3 Premature Withdrawal from the Study Table 1 Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts[Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes #2, #4, #6, #12, #19 Section 9.2.1.1 Informed Consent Section 9.2.2.2 COVID-19 Symptomology (Strict Terms and Broad Terms) Section 9.2.3.1 Targeted Physical Examination and Vital Signs Section 9.2.4 Drug Concentration and Measurements Section 10.1.1 General Guidelines Section 11.2.1 Cohort A- Justification of Sample Size Section 11.4.5.1 Adverse Events Section 13.2 Informed Consent
• Added description that the investigator will recommend that subjects measure their body temperature daily and when they feel unwell. • Revised the description of subject subset 1 and subset 2 to indicate these are completed.	Per protocol, fever is 1 of the signs that define 1 of the primary endpoints of the study (ie, symptomatic SARS-CoV-2 infection). In order to reduce the possibility that study subjects forget to measure their temperature, wording was added to the protocol for investigators to recommend that temperature be measured daily and when subjects feel unwell These subject subsets are completed	Clinical Study Protocol Synopsis: Study Design, Statistical Plan Section 6.1.3 Efficacy Assessment Period Section 6.1.4 Follow-up Period Table 2 Schedule of Events for Drug Concentration, Immunogenicity, and Laboratory Testing Section 10.1.1 General Guidelines Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A) Section 11.4.3.1.3 Secondary Efficacy Analyses

• Revised the description of the automated reminders to being optional if not technically feasible (language barriers, no mobile phone, etc) • Modify the analysis for continuous endpoints from GEE model to ANOVA/ANCOVA model.	The use of automated reminders was made optional in case of technical/operational difficulties/delays in implementation. For continuous endpoints the analysis population consists of those subjects who have at least 1 positive RT-qPCR during EAP instead of all subjects in full analysis set (FAS) (ie, smaller sample size). Thus, the ANOVA model will be used and for change and percent change from baseline endpoints the relevant baseline values will be included as covariate in the model (ie, ANCOVA model).	
• Minor editorial updates -added a statement about anti-drug antibody (ADA) assessment to the synopsis - deleted 'post-baseline' -added and deleted references	Added for consistency with the protocol body Corrected an error Updated the reference list	Clinical Study Protocol Synopsis: Procedures and Assessments Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 19 References

Amendment 2

The primary purpose of this amendment is to remove the requirement for subjects to have at least 48 hours of sustained exposure to the index case. The 48-hour exposure requirement is considered to be too restrictive and not necessary since the subject is expected to be living in the same household with the index case. Additionally, the definition of 'household' was updated to clarify the specific characteristics of a household; the guidance for the conduct of the local diagnostic assay testing at baseline was revised; and the analysis of cohort B was revised to include all subjects at baseline (ie, subjects who are seropositive or seronegative).

Description of Change	Brief Rationale	Section(s) Changed
• Removed requirement for subjects to have sustained exposure to the index case for 'at least 48 hours'	The 48-hour exposure requirement is considered to be too restrictive and not necessary since the subject is expected to be living in the same household with the index case. These changes were made to address feasibility issues.	Clinical Study Protocol Synopsis: Study Design Section 6.1 Study Description and Duration Section 7.2.1 Inclusion Criteria, criterion #2
• Updated the definition of 'household' with specific characteristics.	This change was made to specify the characteristics of a 'household 'that are compatible with the	Section 3.2.2 Subject Population

	assumptions used for the sample size calculation.	
• Revised the description of local diagnostic assay to include SARS-CoV-2 antigen or RT-PCR using an appropriate sample such as nasopharyngeal (NP), nasal, oropharyngeal (OP), or saliva. • Added the option to not perform the local diagnostic assay for SARS-CoV-2 if the results are not anticipated to be available in a timely manner for randomization. • Revised the description of the automated reminders to be 'implemented as soon as technologically feasible' • Revised the Schedule of Events and footnotes to clarify the procedures for subjects who are RT-qPCR negative and the procedures for subjects who are RT-qPCR positive	These changes were made to address feasibility and operational constraints for clinical sites.	Clinical Study Protocol Synopsis, Study Design, Procedures and Assessments Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 5.1 Demographic and Baseline Characteristics Figure 1 Study Flow Diagram Section 6.1 Study Description and Duration Section 6.1.2 Screening/Baseline Section 6.1.3 Efficacy Assessment Period Section 8.4 Method of Treatment Assignment Table 1 Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes - #7, #9, #17, #18, #19, #20 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 9.2.1.2 Local Diagnostic Assay for SARS-CoV-2
• Revised the planned analysis for cohort B to also include subjects who are seropositive at baseline • Updated the cohort B exploratory endpoints • Updated the primary efficacy analysis (cohort A) and secondary efficacy analyses	This change was made since many of the subjects enrolled in cohort B (RT-qPCR positive at baseline) are seropositive at baseline, using semi-quantitative assays, and the presence of antibodies in subjects with an active infection is of unknown clinical relevance.	Clinical Study Protocol Synopsis: Objectives, Endpoints, Statistical Plan Section 2 Study Objectives Section 2.1 Cohort A: SARS-CoV-2 RT qPCR Negative at Baseline Section 2.2 Cohort B: SARS-CoV-2 RT qPCR Positive at Baseline Section 2.2.1 Cohort B Secondary Objectives Section 2.2.2 Cohort B Exploratory Objectives Section 4.1 Cohort A: SARS-CoV-2 RT qPCR Negative at Baseline Section 4.2 SARS-CoV-2 RT-qPCR Positive at Baseline Section 4.2.1 Cohort B Secondary Efficacy Endpoints Section 4.2.2 Cohort B Exploratory Endpoints Section 11.3.1 Full Analysis Sets

		Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A) Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A) Section 11.4.3.1.2 Events that Require Expedited Reporting to Sponsor Section 11.4.3.1.3 Secondary Efficacy Analyses
• Added the caveat that the use of automated reminders for subjects would be implemented if systems allow, as soon as or if feasible.	This change was made to clarify the use of automated reminders in the study.	Section 6.1.3 Efficacy Assessment Period
• Added a summary of safety results from the sentinel safety group of this study	This summary was added to present the safety results.	Section 3.2.1 Study Design
• Revised the description of the Safety Review Committee	Clarified the composition of the Safety Review Committee	Section 6.3.2 Safety Review Committee for REGN 2069/CoVPN3502
• Removed 'electrocardiogram' from the description of results of the sentinel safety group data from earlier studies in the REGN10933+REGN10987 clinical development program	This change is a correction of an error in the description of the assessments for the sentinel safety group.	List of Abbreviations Section 3.2.4 Sentinel Safety Group and Subsequent Safety Reviews Section 3.3 Risk-Benefit
• Revised text describing the measurement and analysis of drug or anti-drug antibodies (ADA) • Updated the footnotes describing the collection of PK and ADA samples	These changes clarify the descriptions related to PK or ADA assessments.	Clinical Study Protocol Synopsis: Endpoints Section 4.1.2 Cohort A Secondary Endpoints Section 5.4 Pharmacokinetic Variables Table 2 Schedule of Events for Drug Concentration, Immunogenicity, and Laboratory Testing Section 9.1.2 Schedule of Events Table 2: Drug Concentrations, Immunogenicity, and Laboratory Testing, Footnotes #6, #7 Section 11.3.3 Pharmacokinetic Analysis Set Section 11.3.4 Immunogenicity Analysis Set
• Added the statement highlighting that for this study only severity grade 3 or above for anaphylaxis, allergic reaction (hypersensitivity reaction), and injection site reaction are reportable as	This change was made to clarify the reporting of AESIs.	Table 4 NCI-CTCAE Severity Grading System for Adverse Events for Anaphylaxis, Allergic Reaction, and Injection Site Reaction

adverse events of special interest (AESIs)		
• Minor editorial update - addition of EudraCT number to the title page - corrected a sentence in the Introduction - minor edits for clarity - study monitoring section updated to match the current protocol template - Risk Management Lead updated to Global Safety Lead to match current nomenclature for role	Throughout	Title Page Section 1.3 The Role of Spike Protein in SARS-CoV-2 Pathogenesis Section 5.2 Efficacy Variables Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS0CoV-2 Infection Section 6.1.1 Sentinel Subjects and Staggered Enrollment/Dosing Section 6.3.2 Safety Review Committee for REGN 2069/CoVPN3502 Section 12.2.1 Monitoring of Study Sites

Amendment 1

The purpose of this amendment is to change the collection of respiratory samples for SARS-CoV-2 reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) from nasal swabs and saliva samples to nasopharyngeal (NP) swab samples due to analysis of data from baseline samples from the REGN10933+REGN10987 treatment studies, where study patients were sampled by NP swabs, nasal swabs, and saliva for side-by-side comparison. NP swabs had markedly better sensitivity to detect SARS-CoV-2 than nasal swabs and saliva samples. Additionally, the requirement for local serology testing at baseline was removed because it is anticipated that most subjects will be negative and local serology testing is not feasible at many sites. In addition, this amendment includes updates to address health authority feedback and collaborator comments.

Description of Change	Brief Rationale	Section(s) Changed
• Changed collection from nasal swabs and saliva samples to nasopharyngeal (NP) swabs for SARS-CoV-2 RT-qPCR test • Removed collection of nasal swab and saliva samples for SARS-CoV-2 RT-qPCR test • Removed endpoints based on analysis of saliva samples for SARS-CoV-2 RT-qPCR test • Clarified that molecular diagnostic RT-PCR tests, qualitative and quantitative, will be unblinded to site personnel and the Sponsor	Based on review of blinded RT-PCR data from REGN10933-10987 treatment studies, use of NP swab samples had better sensitivity to detect RT-PCR positivity than nasal swab and saliva samples. This change is to ensure proper medical care and isolation of positive subjects and to ensure appropriate quality control of NP samples.	Clinical Study Protocol Synopsis: Study Design, Endpoints, Procedures and Assessments, Statistical Plan Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 3.2.5 Primary Objectives Section 4.1.2 Cohort A Secondary Endpoints Section 4.1.3 Cohort A Exploratory Endpoints Section 4.2.1 Cohort B Secondary Endpoints Section 4.2.2 Cohort B Exploratory Endpoints Section 5.2 Efficacy Variables Figure 1 Study Flow Diagram Section 6.1.3 Screening/Baseline Section 6.1.4 Efficacy Assessment Period Section 6.1.5 Follow-up Period Table 3 Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes - #4, #7, #9

		Section 9.2.2.1 Nasopharyngeal Swab SARS-CoV-2 RT-qPCR Test (Central Lab) Section 9.2.2.2 COVID-19 Symptomology (Strict Terms and Broad Terms) Section 9.2.6.1.1 Viral Sequencing Section 9.2.6.2 Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies Section 11.4.1 Subject Disposition Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A) Section 11.4.3.2 Secondary Efficacy Analyses Section 11.4.4.1 Cohort A Section 11.4.4.2 Cohort B Section 11.4.5.1 Adverse Events Section 11.4.5.2 Other Safety (Vital Signs and Laboratory Tests Section 11.4.6.1 Analysis of Drug Concentration Data Section 11.4.7 Pharmacokinetics and Pharmacokinetics /Pharmacodynamics Section 11.5 Interim Analysis
• Removed collection of local serology (onsite) at baseline	The purpose of including local serology testing as a stratification factor for randomization was to improve the relative balance of enrollment of seronegative and seropositive subjects in each of the study arms. However, due to clinical laboratory restrictions, local testing using the lateral flow immunoassay is not feasible at most sites. Additionally, the majority of subjects are expected to be seronegative. Because serology testing will be performed by the central lab, subgroup analyses will be performed using baseline central lab serology data and this analysis will not be affected by the elimination of local serology testing.	Clinical Study Protocol Synopsis: Study Design Section 2 Objectives Section 3.2.1 Study Design Section 3.2.3 Enrollment by Baseline SARS-CoV-2 Infection Section 5.1 Demographic and Baseline Characteristics Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 6.1.3 Screening/Baseline Section 8.4 Method of Treatment Assignment Section 8.5 Blinding Table 3 Schedule of Events (All Cohorts, RT qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes - Footnote #8 (removed) Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit
• Removed mention of the sentinel group from the study REGN10933-10987-COV-2068	The REGN10933-10987-COV-2068 study was not initiated in parallel with 2069;	Figure 1 Study Flow Diagram

	therefore, the sentinel group is based on REGN10933-10987-COV-2069 study only.	Section 6.1.1 Sentinel Subjects and Staggered Enrollment/Dosing
• Specify that index case test results can be from SARS-CoV-2 diagnostic test formats that are approved or have Emergency Use Authorization issued by the US FDA or by local health authority.	To improve the feasibility of enrolling household contacts due to the short window (96 hours) between the collection of the index cases' positive SARS-COV-2 RTPCR diagnostic test sample.	Clinical Study Protocol Synopsis: Study Design, Population Section 3.2.1 Study Design Section 3.2.2 Subject Population Section 6.1 Study Description and Duration Section 7.2 Study Population Section 7.2.1 Inclusion Criteria, criterion #2
• Revised the description of the use of any unused or leftover biological samples collected during the study for exploratory research to indicate that the maximum time period of allowable storage (for both exploratory research samples and pharmacogenomic samples) may be shorter per regional laws and regulations	To clarify the intended use and storage of biological samples collected.	Section 9.2.4 Drug Concentration and Measurements Section 9.2.5 Immunogenicity Measurements and Samples Section 9.2.6 Exploratory Pharmacodynamic/Biomarker Procedures Section 9.2.6.2 Serological Assays for Endogenous Anti-SARS-CoV-2 Antibodies Section 9.2.7 Pharmacogenomic Analysis (Optional)
• Clarify the imputation method for missing RT-qPCR results	revised the rules for imputing results	Clinical Study Protocol Synopsis: Statistical Plan Section 11.4.3.1.1 Primary Efficacy Analysis (Cohort A)
• Added country as a fixed factor in the statistical model • Added a description of the timing of statistical analysis	To address health authority requests.	Clinical Study Protocol Synopsis: Study Design Section 6.2 Planned Interim Analysis Section 11.4.9 Timing of Statistical Analysis
• Clarified the justification of sample size for cohort A	Rationale was strengthened to enhance readability based on collaborator feedback.	Section 11.2.1 Cohort A- Justification of Sample Size
• Added a summary of clinical data from the pooled sentinel cohorts from treatment studies (R10933-10987-COV-2066 and R10933 10987-COV-2067) • Clarified that 'healthy subjects' include the elderly or those with stable chronic illness who are considered fit for the study • Clarified the follow-up period for contraception use • Increased frequency of site and/or investigator contact with	To address collaborator comments.	Section 3.2.4 Sentinel Safety Group and Subsequent Safety Reviews Section 3.3 Risk-Benefit Section 5.3 Safety Variables Section 6.1.3 Screening/Baseline Section 6.1.4 Efficacy Assessment Period Section 6.1.5 Follow-up Period Section 6.3.1 Independent Data Monitoring Committee/Data and Safety Monitoring Board Section 6.3.2 Safety Review Committee for REGN 2069/CoVPN3502

subjects who have confirmed SARS-CoV-2 infection • Increased monitoring time after dosing to assess for hypersensitivity and injection site reactions in all subjects who are not in the sentinel group (which has a 4-hour monitoring window) • Clarified that subjects should contact their local emergency department if they experience a true medical emergency • Removed assessment for absenteeism at the screening/baseline visit • Clarified that pregnant subjects are not withdrawn but are followed for safety • Described the specific data to be collected for subjects with a positive RT-PCR result who have medically attended visits (ED, UCC, hospitalization) • Added a household assessment to collect general information about household members • Clarified who can review study records		Section 7.2.1 Inclusion Criteria, #4 Section 7.2.2 Exclusion Criteria, #8, #12, #14 Section 8.9 Prohibited Medications Table 3 Schedule of Events (All Cohorts, RT-qPCR-Negative and Positive) Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnotes #11, #13, #16 Section 9.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 9.2.1.2 Local Molecular Diagnostic Assay for SARS-CoV-2 Section 9.2.2.3 Assessment of Medically Attended Visits Section 9.2.2.4 Absenteeism Assessment Section 9.2.3.1 Targeted Physical Examination and Vital Signs Section 9.2.3.2 Laboratory Testing
• Clarified the Sponsor access to study results	The Sponsor will not have access to post-baseline patient level study results	Section 8.5 Blinding Section 9.1.1 Schedule of Events Table 1 (All Cohorts, RT-qPCR-Negative and Positive) Footnote #14
• Added ethics committee text relevant sections	The study may include sites in other countries	Section 10.4 Notifying Health Authorities, Institutional Review Board/Ethics Committee and Investigators Section 12.3 Audits and Inspections Section 13.2 Informed Consent Section 13.4 Institutional Review Board/Ethics Committee Section 15.2 Close-out of a Site Section 20 Investigator's Agreement

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-Cov-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2

Compound:	REGN10933+REGN10987
Protocol Number:	R10933-10987-COV-2069
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	1.0/25MAR2021

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

See appended electronic signature page

Study Biostatistician [redacted])

See appended electronic signature page

Study Pharmacokinetics [redacted])

See appended electronic signature page

Study Bioanalytical Sciences [redacted]

See appended electronic signature page

Study Medical Director [redacted]

See appended electronic signature page

Project Biostatistician [redacted]

See appended electronic signature page

Head of BDM or designee [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
EAP	Efficacy assessment period
EOS	End of study
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized estimation equation
ICF	Informed consent form
ICH	International Council for Harmonisation
IWRS	Interactive web response system
mAb	Monoclonal antibody
NAb	Neutralizing anti-drug antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
PK	Pharmacokinetic
PCSV	Potentially clinically significant value
RBC	Red blood cell
RBD	Receptor binding domain
RT-qPCR	Quantitative reverse transcription polymerase chain reaction (test; refers to the central lab testing in this protocol)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock and unblinding. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R10933-10987-COV-2069 study. The SAP includes multiple steps of analyses described in Section 7.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on blinded data review, and a final plan will be issued prior to the first step database lock and unblinding of the individual treatment assignment.

1.1. Background/Rationale

This study will assess the use of REGN10933+REGN10987 in preventing household transmission of SARS-CoV-2. A household is defined as a group of people who live together at the same residence and share multiple living spaces (e.g., living room, bedroom, kitchen, bathroom).

1.2. Study Objectives

All subjects in the study will have household contact with the first household member known to be infected with SARS-CoV-2 infection (index case) but who are themselves either not infected or who are asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening. In this study, the household contact must share the same residence and have a close exposure to the first individual in the household with a known SARS-CoV-2 infection (index case).

For the analyses, there are four cohorts defined based on the subject's SARS-CoV-2 infection status at baseline, as measured by central lab SARS-CoV-2 RT-qPCR (quantitative reverse transcription polymerase chain reaction), and on the subject's age:

- For subjects with SARS-CoV-2 RT-qPCR negative at baseline, they are assigned into two cohorts:
  - Cohort A (adult and adolescent subjects [≥12 years])
  - Cohort A1 (pediatric subjects [<12 years])

or

- For subjects with SARS-CoV-2 RT-qPCR positive at baseline, they are assigned into two cohorts:
  - Cohort B (adult and adolescent subjects [≥12 years])
  - Cohort B1 (pediatric subjects [<12 years])

1.2.1. Primary Objectives

The primary objectives are for subjects who are seronegative at baseline (based on central lab test) unless stated otherwise.

Efficacy – Cohort A (Adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR negative at baseline)

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR

Efficacy – Cohort B (Adult and adolescent subjects (≥12 years) who are SARS-CoV-2 RT-qPCR positive at baseline)

- To evaluate the efficacy of REGN109333+REGN10987 compared to placebo in preventing COVID-19 symptoms (broad-term)

Safety – Cohort A and Cohort A1, Cohort B and B1

To evaluate the safety and tolerability of REGN10933+REGN10987 following subcutaneous (SC) administration compared to placebo

1.2.2. Secondary Objectives

Cohort A and Cohort A1

The following secondary objectives are for subjects who are seronegative at baseline (based on central lab test) unless stated otherwise.

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing a SARS-CoV-2 infection with a high viral load (i.e. viral load >4 (log10 copies/mL))
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load (i.e. viral load >4 (log10 copies/mL))
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing asymptomatic or symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of treating the index case with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among their household contacts in placebo group (note: This is a cross-study analysis based on only subjects in placebo group of R10933-10987-COV-2069 whose index cases participated in R10933-10987-COV-2067)

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (Centers for Disease Control and Prevention (CDC) definition) confirmed by RT-qPCR
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (strict-term) confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To evaluate the impact of treating any SARS-CoV-2 RT-qPCR positive household member with REGN10933+REGN10987 on the incidence of SARS-CoV-2 infection among their household contacts in placebo group (note: This is a cross-study analysis based on only subjects in placebo group of R10933-10987-COV-2069 whose index or other household member participated in R10933-10987-COV-2067 or in cohort B)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration in seropositive subjects
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated seronegative and seropositive subjects compared with placebo-treated subjects
- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing symptomatic SARS-CoV-2 infection (broad-term) confirmed by RT-qPCR (cohort A1)

<u>Cohort B and Cohort B1</u>

Secondary objectives for Cohort B and Cohort B1 are for all seronegative subjects at baseline (by central lab test) unless stated otherwise.

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing development of:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term; cohort B1)
  - Symptomatic SARS-CoV-2 infection (CDC definition)

- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of SARS-CoV-2 infection with a high viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on SARS-CoV-2 viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 infection:
- On health care utilization
- On absenteeism from daily responsibilities (where applicable)
- To characterize the drug concentration-time profiles of REGN10933 and REGN10987 in serum and selected PK parameters
- To assess the immunogenicity of REGN10933 and REGN10987
- To evaluate the safety and tolerability of REGN10933+REGN10987 following SC administration
- To estimate the incidence and severity of symptomatic SARS-CoV-2 infection over time, including the period following study drug treatment, in REGN10933+REGN10987-treated subjects compared with placebo-treated subjects

1.2.3. Exploratory Objectives

<u>Cohort A and Cohort A1</u>

- To evaluate the efficacy of REGN10933+REGN10987 compared to placebo in preventing SARS-CoV-2 infection assessed by seroconversion in baseline seronegative subjects
- To explore the impact of REGN10987+REGN10933 compared to placebo:
  - On humoral immune response to SARS-CoV-2 infection
  - On measures of infectivity of SARS-CoV-2 as assessed in experimental laboratory assays
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in SARS-CoV-2 infection in subjects who are seropositive at baseline:
  - Prevention of symptomatic infection (strict-term)
  - Prevention of symptomatic infection (broad-term)
  - Prevention of symptomatic infection (CDC definition)
  - Prevention of asymptomatic infection or symptomatic re-infection (strict-term, CDC definition, or broad-term)

- To explore the relationships between REGN10933+REGN10987 exposure and selected clinical efficacy and safety endpoints and/or biomarkers in seropositive and seronegative subjects
- To assess viral genetic variation in SARS-CoV-2 in subjects with a positive SARS-CoV-2 RT-qPCR
- To explore biomarkers (including host genome variants) associated with safety and efficacy of REGN10933+REGN10987 and to study SARS-CoV-2 (cohort A only)
- To evaluate the impact of treating any household member with anti-SARS CoV-2 monoclonal antibody on the incidence of SARS-CoV-2 infection among their household contacts. The monoclonal antibody treatment considered for this analysis are any EUA approved antibody including REGN10933+REGN10987 (within or outside of the study R10933-R10987-COV-2067)

Cohort B and Cohort B1

- To evaluate the impact of REGN10933+REGN10987 compared to placebo in seropositive subjects in preventing:
  - Symptomatic SARS-CoV-2 infection (strict-term)
  - Symptomatic SARS-CoV-2 infection (broad-term)
  - Symptomatic SARS-CoV-2 infection (CDC definition)
- To evaluate the impact of REGN10933+REGN10987 compared to placebo on the duration of signs and symptoms in seropositive subjects with symptomatic SARS-CoV-2 infection confirmed by RT-qPCR
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in seropositive subjects on SARS-CoV-2 RT-qPCR viral load
- To evaluate the impact of REGN10933+REGN10987 compared to placebo in seropositive subjects on SARS-CoV-2 infection:
  - On health care utilization
  - On absenteeism from daily responsibilities (where applicable)
- To explore the impact of REGN10987+REGN10933 compared to placebo in subjects, by their baseline serology test status (e.g., seropositive or seronegative, based on central lab test) on SARS-CoV-2 infection:
  - On humoral immune response
  - On measures of infectivity of SARS-CoV-2 as assessed in experimental laboratory assays
- To explore the relationships between REGN10933+REGN10987 exposure and selected clinical efficacy and safety endpoints and/or biomarkers in seropositive and seronegative subjects

- To assess viral genetic variation in SARS-CoV-2 in subjects with a positive SARS-CoV-2 RT-qPCR.
- To explore biomarkers (including host genome variants) associated with safety and efficacy of REGN10933+REGN10987 and to study SARS-CoV-2

1.2.4. Modifications from the Statistical Section in the Final Protocol

There are no modifications compared to protocol amendment 6.

1.2.5. Revision History for SAP Amendments

This is the first version of SAP.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a phase 3 randomized, double-blind, placebo-controlled study in adults/adolescent subjects (≥12 years) and pediatric subjects (<12 years of age) who are household contacts of the first known household member infected with SARS-CoV-2 (index case). All subjects in the study are asymptomatic (having no active respiratory or non-respiratory symptoms consistent with COVID-19) at the time of screening. The index case will have a diagnosis of SARS-CoV-2 infection using a diagnostic test, e.g., RT-PCR, antigen test, or other test format (approved or with Emergency Use Authorization issued by the US FDA or by local health authority). Randomization will be performed by individual study subjects, not by households. Some of the index cases of household contacts in this study may be participating in a separate treatment study (R10933-10987-COV-2067).

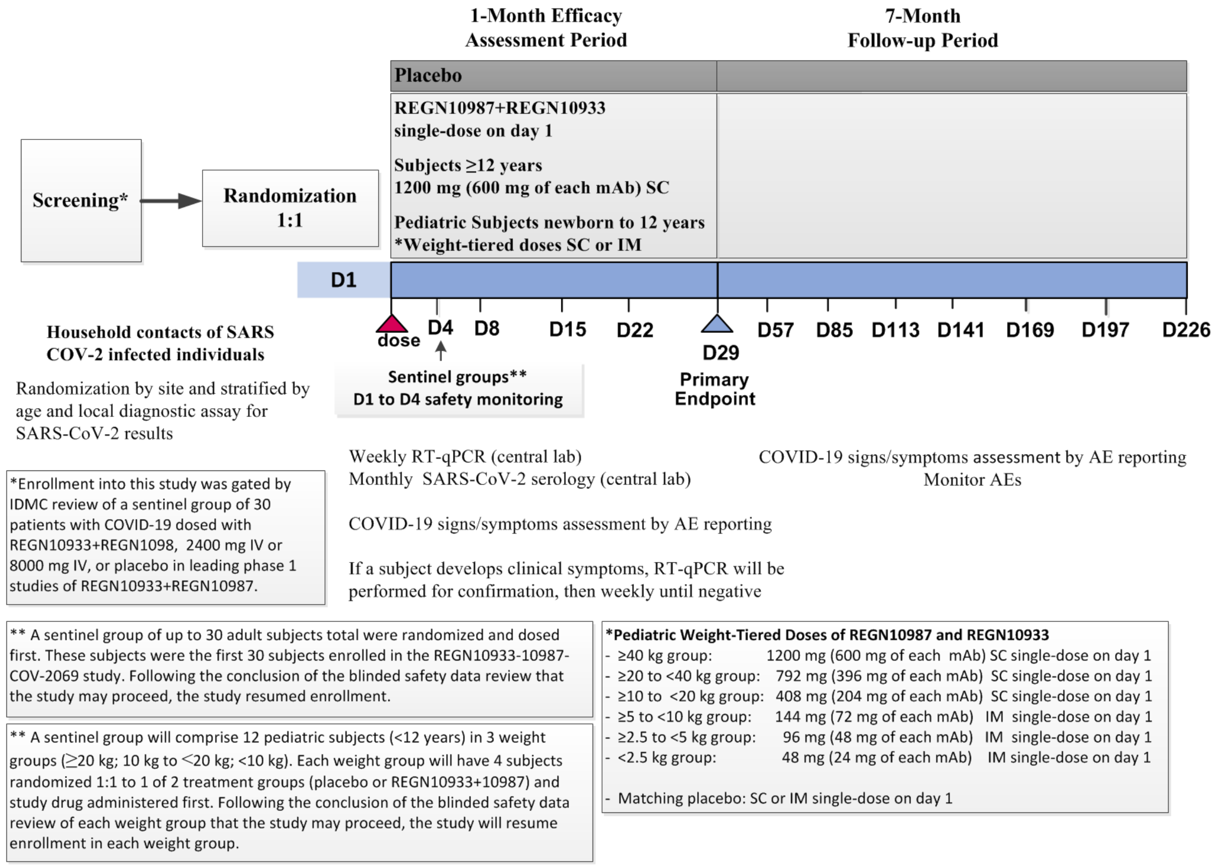
Randomization will be performed by site and stratified for assigning subjects in a 1:1 allocation ratio to placebo or REGN10933+REGN10987 [1200 mg (600 mg of each mAb SC). Randomization stratifications are test results (positive, negative, or unavailable) of a local diagnostic assay for SARS-CoV-2 (e.g., molecular assay such as RT-PCR assay for SARS-CoV-2 or a SARS-CoV-2 antigen test) from appropriate samples, e.g., nasopharyngeal (NP), oropharyngeal (OP), nasal, or saliva, and age group (<12 years, ≥12 to <18 years, ≥18 to <50 years, or ≥50 years). For pediatric subjects (<12 years), the weight group (≥20 kg, ≥10 to <20 kg, and <10 kg) will be used as an additional stratification factor.

The study was originally planned to enroll 2000 adult and adolescent subjects. A blinded analysis of approximately 25% of enrolled subjects in this study was performed, demonstrating that higher than expected seropositivity was observed in cohort A. In addition, an unblinded administrative analyses was performed on the data based on 554 subjects to verify assumptions and adequacy of sample size. The subjects who were included in the administrative assessment will not be included in the final efficacy analysis. Thus, sample size was increased to accommodate higher seropositivity rate and the unblinded administrative assessment. The total study population was planned to be approximately 3500 adult and adolescent subjects (~3150 subjects in cohort A and ~350 subjects in cohort B) including 554 cohort A subjects in the administrative assessment and approximately 250 pediatric subjects <12 years old (~225 subjects in cohort A1 and 25 subjects in cohort B1), with household contact exposure to individual with a confirmed SARS-CoV-2 infection.

Statistical analyses will be conducted separately in each cohort. For the purpose of the study analysis, cohorts A, A1, B, and B1 are independent. As specified earlier, the 554 subjects in the administrative assessment will not be included in the final efficacy analyses (first step analysis) however, these subjects will be included in the safety analyses. Also, the final efficacy analysis (first step analysis) will include only subjects randomized on or before January 28, 2021. The total number of subjects to be included in the first step analysis is approximately 2459. The subjects randomized after January 28, 2021 will remain blinded until the final analysis but will not be part of any formal statistical testing.

For each subject, the study comprises 3 periods: a 1-day screening/baseline period, a 1-month EAP, and a 7-month follow-up period (See Figure 1).

Figure 1: Study Flow Diagram



The schedule of events tables for this study can be found in the Appendix 10.2.

2.2. Sample Size and Power Considerations

2.2.1. Cohort A

The primary hypothesis is the reduction in the proportion of symptomatic RT-qPCR (broad-term) confirmed SARS-CoV-2 infections in seronegative subjects. To calculate the sample size to achieve at least 90% power for seronegative subjects in cohort A, it is assumed that the statistical hypothesis will be tested in a 2-sided test. Based on the administrative assessment results among 409 seronegative subjects in cohort A, an approximately 50% reduction of infection (symptomatic or asymptomatic) compared to placebo group and a 100% reduction of symptomatic infection compared to placebo group was observed. Due to the small sample size in the administrative assessment, it was assumed, for the purpose of assessing study power, that an approximately 50% reduction or greater in symptomatic infections compared to the placebo group will be expected for the final primary efficacy analysis.

In this household study design, the number of subjects per household, the correlation between subjects and symptomatic infection rates within a household are unknown. To detect a relative risk of 0.5 (i.e., 50% reduction of the assumed 10% attack rate in the placebo arm), equivalent to an odds ratio of 0.47, power was calculated compared to the p-value of 0.05 based on 2000 simulations in 1248 subjects from 430 households (i.e., assuming an average household size of 2.9 seronegative subjects). Table 1 provides power calculations by varying degrees of correlation within household. In all cases, the power of the study is >90% using a generalized linear model with the generalized estimation equation (GEE) approach assuming a compound symmetry covariance matrix.

Table 1: Simulated Power for Household Design (1248 Subjects over 430 Households)

Placebo Attack Rate	REGN10933+ REGN10987 Attack Rate	Correlation within Household	Average Odds Ratio REGN10933+REGN10987 versus Placebo	Power
10%	5%	0.1	0.485	0.914
10%	5%	0.2	0.485	0.934
10%	5%	0.3	0.480	0.956
10%	5%	0.4	0.481	0.972
10%	5%	0.5	0.476	0.983
10%	5%	0.6	0.478	0.999

At least 1980 subjects will need to be enrolled in cohort A to have a minimum of 1248 seronegative subjects, assuming that 10% of subjects drop out, and 30% of subjects are seropositive at baseline.

The correlation among subjects within each household, the rates for seronegativity, and the rates for seropositivity will be monitored in a blinded fashion. The 2 assumptions, that 90% of randomized subjects will have a baseline negative RT-qPCR and be assigned to cohort A and that 70% of these subjects in cohort A are seronegative, will be monitored periodically to ensure that there will be a sufficient number of seronegative subjects (~1248) enrolled in Cohort A to be included in the primary analysis. This will maintain the planned statistical power.

2.2.2. Cohort B

The primary endpoint in asymptomatic seronegative subjects in cohort B is the proportions of subjects who subsequently develop signs and symptoms (broad term) within 14 days of a positive RT-qPCR test result at baseline or during the EAP.

The sample size of Cohort B is based on the frequency of finding positive subjects while enrolling Cohort A and assumes that approximately 10% of subjects in a household are already positive for SARS-CoV-2 by RT-qPCR at baseline. Among approximately 3500 adult and adolescent subjects that will be enrolled in cohort A or cohort B, the number of subjects expected in Cohort B is approximately 220 or higher, including 200 seronegative subjects. Assuming that 50% of infected placebo subjects at baseline will develop symptoms, 200 seronegative subjects in cohort B will provide >90% power to detect a relative risk of 0.5, using a 2-sided Fisher's exact test at an alpha level of 0.05.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis.

3.1. The Efficacy Analysis Sets

Seronegative Modified Full Analysis Set (Seronegative mFAS-A) – Cohort A

The seronegative modified full analysis set for Cohort A (Seronegative mFAS-A) includes all randomized subjects aged 12 years and older who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects included in the administrative assessment analysis are excluded from the Seronegative mFAS-A population.

Subjects will be analyzed based on the randomized treatment assignment. The seronegative mFAS-A population is the primary analysis population for the primary and secondary endpoints for Cohort A of this study unless specified otherwise.

Note: There are three antibody assays used for serology test: EuroImmun anti-S IgA, EuroImmun anti-S IgG, and Abbott anti-N IgG (Architect). Seronegative is defined as all available test results are negative. Seropositive is defined as 1 or more available test results are positive.

Seronegative Modified Full Analysis Set (Seronegative mFAS-A1) – Cohort A1

The seronegative modified full analysis set for Cohort A1 (seronegative mFAS-A1) includes all randomized subjects aged less than 12 years who are laboratory confirmed negative for SARS-CoV-2 (per central lab PCR test) and who test negative for antibodies for SARS-CoV-2 (per central lab serology testing) at baseline.

Subjects will be analyzed based on the randomized treatment assignment. The efficacy endpoints for Cohort A1 will be analyzed using the seronegative mFAS-A1 unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B) – Cohort B

The seronegative modified full analysis set for Cohort B (seronegative mFAS-B) includes all randomized subjects aged 12 years and older who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) at baseline and are asymptomatic. Subjects will be analyzed based on the randomized treatment assignment. The primary and secondary efficacy endpoints for cohort B will be analyzed using the seronegative mFAS-B unless specified otherwise.

Seronegative Modified Full Analysis Set (Seronegative mFAS-B1) – Cohort B1

The seronegative modified full analysis set for Cohort B1 (seronegative mFAS-B1) includes all randomized subjects aged less than 12 years who have laboratory confirmed positive tests at baseline for SARS-CoV-2 RT-qPCR and negative SARS-CoV-2 serology (both based on central lab testing) at baseline and are asymptomatic. Subjects will be analyzed based on the randomized treatment assignment. The efficacy endpoints for Cohort B1 will be analyzed using the seronegative mFAS-B1 unless specified otherwise.

3.2. The Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all randomized subjects who received at least 1 dose or part of a dose of study drug. Subjects in the SAF will be analyzed based on the treatment received (as treated). In general, safety will be evaluated by study cohort: SAF-A (Cohort A), SAF-B (Cohort B), SAF-A1(Cohort A1), and SAF-B1 (Cohort B1). However, injection site reactions will also be based on all cohorts combined.

3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all subjects who received any study drug and who had at least 1 non-missing drug concentration measurement following study drug administration. Subjects will be analyzed based on actual treatment received.

3.4. Immunogenicity Analysis Sets

3.4.1. Anti-drug Antibodies Analysis Set

The ADA analysis set (AAS) includes all subjects who received study drug and had at least 1 non-missing ADA result after study drug administration. Subjects will be analyzed based on the actual treatment received

3.4.2. Neutralizing Antibody Analysis Set

The NAb analysis set (NAS) includes all subjects who received any study drug and who are either negative in the ADA assay or positive for ADA with at least one non-missing result in the NAb assay after first dose of the study drug. Subjects who are ADA negative are set to negative in the NAb analysis set. Subjects will be analyzed according to the treatment actually received.

4. ANALYSIS VARIABLES

For each subject, demographic and baseline characteristics will be obtained from the last available value up to the date of the first study treatment administration (i.e., baseline definition). For subjects randomized but not treated, the baseline value is defined as the last available value prior to or on the date of randomization. If a subject was randomized over once, the latest randomization record will be used for analysis.

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized:

- Age in years (continuous and categorical variable for subjects≥12 years will be categorized as follows: ≥12 to <18, ≥18 to <50, ≥50 to <65, ≥65 to <80, ≥80 years)
- Sex (Male, Female)
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other, where "Other" may include, for example, not reported, unknown, and multiracial, etc.)
- Ethnicity (Hispanic or Latino with further subgroups [Black Hispanic or Latino and White Hispanic or Latino], not Hispanic or Latino with further subgroups [Black not Hispanic or Latino and White not Hispanic or Latino], not reported, and unknown)

Baseline characteristic variables include:

- Weight (kg) (quantitative and qualitative variable for pediatric subjects: <10, ≥10 to <20, and ≥20)
- Height (cm)
- Body mass index (BMI) (kg/m^2) (quantitative and qualitative variable for subjects ≥12 years: <30 and ≥30)
- Randomization strata: local RT-qPCR status and age
- Region (US vs ex-US) and country
- Total household size including the house member(s) not participating this study
- Number of study subjects within household and cohort
- Index case interaction and household risk factors (e.g., share a bedroom, share a common room, no one wears a mask in home, etc.) per eCRF
- Status of index case participating R10933-10987-COV-2067
- Total household members, including index case, who participate the R10933-10987-COV-2067
- Infection risks (e.g. healthcare worker (Yes/ No), received influenza vaccine in last 14 days (Yes/No), first responder (Yes/No), Need to contact strangers on a regular basis (Yes/No), etc.) per exposure risk factors eCRFs

- Baseline overall serology status and observed combinations of three serology antibody assays
- Viral load (log10 copies/mL) at baseline for subject in cohort B
- Days between baseline central RT-qPCR test and study drug administration
- Baseline high risk subjects with at least one of the following criteria:
  - ≥65 years of age
  - BMI ≥35
  - Chronic kidney disease
  - Diabetes
  - Immunosuppressive disease
  - Are currently receiving immunosuppressive treatment

Are ≥55 years of age AND have cardiovascular disease OR hypertension OR chronic obstructive pulmonary disease

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA®).

4.3. Pre-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD, Drug Global version SEP2020 B3). Subjects will be counted once in all ATC categories linked to the medication.

<u>Prior medications/procedures:</u> medications taken, or procedures performed prior to administration of the first study drug.

<u>Concomitant medications/procedures during treatment-emergent EAP:</u> medications taken or procedures performed in the period from the day of the first dose of study drug to 28 days after the last dose of study drug or to the last visit if a subject discontinue from the study, whichever is earlier. This includes medications that were started before the initiation of study treatment and are ongoing during the treatment-emergent EAP.

<u>Concomitant medications/procedures during the treatment-emergent follow-up period:</u> medications taken, or procedures performed from the day after the end of treatment-emergent EAP to the final study visit or started during the treatment-emergent EAP and are ongoing after treatment-emergent EAP.

4.4. Prohibited Medications

The definition of prohibited medications is described in the section 8.9 of the protocol. They will be reviewed and identified by the study clinician and reported in protocol deviations.

4.5. Efficacy Variable

Unless otherwise specified, the baseline assessment is the last available measurement prior to the date of the study treatment administration. For subjects randomized but not treated, the baseline value is defined as the last available value prior to the date of randomization. Unless otherwise specified, all efficacy endpoints will be analyzed based on seronegative subjects in the corresponding cohort.

The definitions of broad-term, strict-term, and CDC definition symptoms are as follows:

Strict term:

- Fever (≥38°C) PLUS ≥1 respiratory symptom (sore throat, cough, shortness of breath)

OR

- 2 respiratory symptoms (sore throat, cough, shortness of breath)

OR

- 1 respiratory symptom (sore throat, cough, shortness of breath) PLUS ≥2 non-respiratory symptoms (chills, nausea, vomiting, diarrhea, headache, conjunctivitis, myalgia, arthralgia, loss of taste or smell, fatigue or general malaise)

Broad term:

ANY of the following:

1. Fever ≥38°C
2. Feverish
3. Sore throat
4. Cough
5. Shortness of breath/difficulty breathing *(nasal flaring*)*
6. Chills
7. Nausea
8. Vomiting
9. Diarrhea
10. Headache
11. Red or watery eyes *(conjunctivitis)*
12. Body aches such as muscle pain or joint pain *(myalgia, arthralgia)*
13. Loss of taste/smell
14. Fatigue *(fatigue or general malaise or lethargy*)*
15. Loss of appetite or poor eating/feeding
16. Confusion
17. Dizziness
18. Pressure/tightness in chest
19. Chest pain

20. Stomachache (*Abdominal pain**)
21. Rash
22. Sneezing
23. Runny nose
24. Sputum/phlegm
25. Other

**Signs and symptoms observed in pediatric subjects (age<12 years)*

CDC definition

At least two of the following symptoms: fever (measured, i.e., fever ≥38°C, or subjective, i.e., feverish), chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion or runny nose

OR

Any one of the following symptoms: cough, shortness of breath, difficulty breathing, new olfactory disorder, new taste disorder

OR

Severe respiratory illness with at least one of the following, clinical or radiographic evidence of pneumonia, acute respiratory distress syndrome (ARDS)

Note: Fever information will be collected from the fever assessment eCRF, and signs and symptoms will be collected from COVID-19 symptoms eCRF.

The following general rules will be used for efficacy variables and all SARS-CoV-2 RT-qPCR test results are based on the central lab testing:

- For cohort determination, qualitative PCR results from swabs taken prior to or within 2 hours of study drug administration will be used if there are no available test results prior to study drug administration.
- Quantitative values of viral load will be determined based on NP swabs only. For baseline viral load, only RT-qPCR results from swabs taken prior to dosing will be used.
- A positive infection will be defined based on any available RT-qPCR result (either NP, nasal or saliva) which is reported as “detected”. A negative infection will be defined based on all available RT-qPCR results (either NP, nasal or saliva) which are reported as “not detected”.
- Symptomatic SARS-CoV-2 infection (broad-term) is defined as a positive central lab SARS-CoV-2 RT-qPCR result (either NP, nasal or saliva) associated with signs and symptoms with the onset date occurring within 14 days of a positive RT-qPCR during the EAP.
- For subjects in Cohort B, symptomatic SARS-CoV-2 infection (broad-term) is defined as having at least one signs and symptoms with the onset date occurring within 14 days of a positive RT-qPCR (either NP, nasal or saliva) at baseline or during the EAP.

- Viral loads less than the lower limit of quantification of the PCR assay but with positive qualitative results will be set to half of the lower limit of quantification of the PCR assay; values with nondetectable RNA will be set to 0 $\log_{10}$ copies/mL Viral load values above the upper limit of quantification will be re-tested using the reflex test and the corresponding quantitative value will be used in the analysis.

4.5.1. Cohort A Primary Efficacy Variable

The primary efficacy variable in Cohort A is:

- Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP

A symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP will be any positive post-baseline RT-qPCR obtained during the EAP in which the subject experiences COVID-19 related signs or symptoms within 14 days of a positive test.

4.5.2. Cohort A Key Secondary Efficacy Variables

The key secondary efficacy variables listed below include two types of variables: binary (B) and continuous (C) variables.

Key Secondary Efficacy Variables	Type	Cohort A
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP	B	X
Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP	C	X
Number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples during the EAP	C	X
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	C	X
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	B	X
Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in Study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 vs placebo in Study R1033-10987-COV-2067)	C	X

Duration of symptomatic infection (weeks) is defined as (the end date of all symptoms minus the date of the first symptom+1)/7, where a symptom is defined in Section 4.5. If the symptom is ongoing at the time of the first step analysis, the end date of the symptom will be set as the cutoff date for the first step analysis.

4.5.3. Cohort A and Cohort A1 Other Secondary Efficacy Variables

The secondary efficacy variables listed below include two types of variables: binary (B) and continuous (C) variables and marked for the corresponding cohort.

Other Secondary Efficacy Variables	Type	Cohort	
		A	A1
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (CDC definition) during the EAP	B	X	X
Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (CDC definition) during the EAP	C	X	X
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (strict-term) during the EAP	B	X	X
Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (strict-term) during the EAP	C	X	X
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection at each week in the EAP	B	X	X
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad term) at each week in the EAP	B	X	X
Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the third weekly visit after the first positive test during the EAP *Note: Only for RT-qPCR positive subjects during the EAP in the Seronegative mFAS-A set*	C	X	X
Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab samples (that has an onset during the EAP) until the second weekly visit after the first positive test during the EAP *Note: Only for RT-qPCR positive subjects during the EAP in the Seronegative mFAS-A set*	C	X	X
Maximum SARS-CoV-2 RT-qPCR viral load (log10 viral copies/mL) in NP swab samples among individuals with ≥1 RT-qPCR positive that has an onset during the EAP	C	X	X
SARS-CoV-2 RT-qPCR viral load (log10 viral copies/mL) in NP swab samples corresponding to the onset of first positive RT-qPCR during the EAP	C	X	X
Area under the curve (AUC) in viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR NP swab samples detected during the EAP until the first confirmed negative test (testing that occurs after the EAP will be included if necessary to achieve a negative test result).	C	X	X

Note: Only for RT-qPCR positive subjects during the EAP in the Seronegative mFAS-A set			
Number of medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	C	X	X
Proportion of subjects with at least one COVID-19 related hospitalization or emergency room visit associated with a positive RT-qPCR during the EAP, or all-cause death	B	X	X
Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	B	X	X
Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	B	X	X
Number of days of hospital and intensive care unit (ICU) stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	C	X	X
Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (students), daycare or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset during the EAP	C	X	X
Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with at least one household member participating either in R10933-10987-COV-2067 or in cohort B (comparison of those whose households members receive REGN10933+REGN10987 vs placebo in R1033-10987-COV-2067 or in Cohort B)	B	X	X
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP	B		X
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP	B		X
Number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) during the EAP	C		X
Number of weeks of high-viral load >4 (log10 copies/mL) in NP swab samples during the EAP	C		X
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	C		X
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP	B		X

Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 vs placebo in R1033-10987-COV-2067)	C		X

Time-weighted average (TWA) of viral load (log10 copies/mL) in NP swab samples from the day of the first positive SARS-CoV-2 RT-qPCR (central lab) to the third weekly visit after the first positive test visit: all observed viral load data from the first positive visit to the third weekly visit will be calculated using the trapezoidal rule as the area under the curve divided by this observational period as follows:

$$TWA = AUC/(t_k - t_1) = [\sum_{i=2}^{k=3}(t_i - t_{i-1}) * (V_i + V_{i-1})/2]/(t_k - t_1)$$

where V_i is the result of viral load (log10 copies/mL) at time point t_i. V_1 is the result of the viral load (log10 copies/mL) for the first positive SARS-CoV-2 RT-qPCR at timepoint t_1. If the V_i is not available at the scheduled time point t_i or missing due to failed test or other reasons, only the time points with non-missing values will be included for TWA calculation. If there are duplicate samples at a time point, the highest viral result will be used for analysis.

Note: For TWA of viral from the first positive to the second weekly visit after the first positive test visit endpoint, all observed viral load data from the first positive visit to the second weekly visits will be calculated using the same formula described above.

4.5.4. Cohort A and Cohort A1 Exploratory Efficacy Variables

The following exploratory variables are for both Cohort A and Cohort A1. Some of the endpoints will mature and be assessed after all subjects complete the study. For continuous variables the analysis only applies to subjects who have a positive central lab SARS-CoV-2 RT-qPCR test (based on observed data) during the EAP.

Exploratory Variables	Type
Proportion of baseline-seronegative subjects who have a first RT-qPCR confirmed SARS-CoV-2 infection in the follow-up period (i.e. after Day 29 visit)	B
Proportion of baseline-seronegative subjects who become seropositive (based on central lab test) up to day 57 (Note: For post-treatment serology, only antibody assay(s) that do not bind to REGN10933 or REGN10987 will be used to define the endpoint)	B
Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP	B
Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of the serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP	B

Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (strict-term) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP	B
Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (broad-term) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP	B
Proportion of subjects with negative RT-qPCR (based on central lab test) regardless of serology status at baseline who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seronegative or baseline-seropositive subjects with negative RT-qPCR (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR and symptomatic (CDC definition) SARS-CoV-2 infection during the EAP	B
Proportion of baseline-seropositive subjects (based on central lab test) who subsequently have a positive SARS-CoV-2 RT-qPCR during the EAP	B
Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab sample (that has an onset during the EAP) until third weekly visit after the first positive test in seropositive subjects (based on central lab test) during the EAP	C
Time-weighted average of viral load (log10 copies/mL) from the first positive SARS-CoV-2 RT-qPCR in NP swab sample (that has an onset during the EAP) until the second weekly visit after the first positive test in seropositive subjects (based on central lab test) during the EAP	C
Area under the curve (AUC) in viral load (log10 copies/mL) in NP swab samples from the first positive SARS-CoV-2 RT-qPCR NP swab sample until the first confirmed negative test, in seropositive subjects (based on central lab test) that has an onset during the EAP *Note: Only for RT-qPCR positive subjects during the EAP with confirmed negative tests in the seronegative mFAS*	C
Proportion of subjects in placebo group who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members participating in study R10933-10987-COV-2067 and receiving REGN10933+REGN10987 or whose household member did not receive treatment with REGN10933+REGN10987	B
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members participating in study R10933-10987-COV-2067 and receiving REGN10933+REGN10987	B
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members receiving an approved monoclonal antibody treatment for COVID-19	B

Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP by the status of household members receiving an approved monoclonal antibody treatment for COVID-19 or REGN10933+REGN10987 in study R10933-R10987-COV-2067	B
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have asymptomatic infection during the EAP	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have symptomatic infection during the EAP	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have a medically attended visit	C

4.5.5. Cohort B Primary Efficacy Variable

The primary efficacy variable for Cohort B is:

- Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

4.5.6. Cohort B Key Secondary Efficacy Variables

The key secondary efficacy variables listed below are continuous (C) variables.

Key Secondary Efficacy Variables	Type
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	C
Number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples during the EAP	C

4.5.7. Cohort B and Cohort B1 Other Secondary Efficacy Variables

The secondary efficacy variables listed below include two types of variables: binary (B) and continuous (C) variables and marked for the corresponding cohort.

Other Secondary Efficacy Variables	Type	Cohort	
		B	B1
Proportion of subjects who subsequently develop signs and symptoms (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP	B	X	X
Proportion of subjects who subsequently develop signs and symptoms (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	B	X	X

Number of weeks of symptomatic SARS-CoV-2 infection (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP	C	X	X
Number of weeks of symptomatic SARS-CoV-2 infection (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	C	X	X
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP	B	X	X
Change in viral load (log10 copies/mL) from baseline to Day 8 visit in NP swab samples	C	X	X
Change in viral load (log10 copies/mL) from baseline to Day 15 visit in NP swab samples	C	X	X
Time-weighted average change from baseline in viral load (log10 copies/mL) in NP swab samples until the Day 22 visit	C	X	X
Area under the curve (AUC) in viral load (log10 copies/mL) in NP swab samples from baseline to the first confirmed negative test	C	X	X
Maximum SARS-CoV-2 RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP	C	X	X
Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP	C	X	X
Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP	B	X	X
Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP	B	X	X
Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP	C	X	X
Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school	C	X	X

(students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection that has an onset at baseline or during the EAP			
Proportion of subjects with at least one COVID-19 related hospitalization or emergency room visit associated with a positive RT-qPCR at baseline or during the EAP, or all-cause death	B	X	X
Proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	B		X
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP	C		X
Number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples during the EAP	C		X

Time-weighted average (TWA) of change from baseline in viral load until the Day 22 visit: All observed viral load data from baseline to Day 22 visit will be calculated for each subject using the trapezoidal rule as the AUC for change from baseline at each time point divided by the time interval of this observational period as follows:

$$TWA = AUC/(t_k - t_1) = [\sum_{i=2}^{k=4}(t_i - t_{i-1}) * (D_i + D_{i-1})/2]/(t_k - t_1)$$

Where D_i is the change from baseline (t_1) in viral load (log10 copies/mL) obtained at time t_i and D_1 =0. If the D_i is not available or missing due to failed test or other reasons, only the time points with non-missing values will be included for TWA calculation. If there are duplicate samples at a time point, the highest viral result (log10 copies/ml) will be used for analysis.

For TWA of percent change from baseline, variable Pi will be applied to the formula above instead of Di, where Pi=Di/baseline.

4.5.8. Cohort B and Cohort B1 Exploratory Variables

The following exploratory variables are for both Cohort B and Cohort B1.

Exploratory Variables	Type
Proportion of subjects who subsequently have symptomatic (strict-term) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to their baseline serology test status (i.e., seropositive or other, based on central lab test)	B

Proportion of subjects who subsequently have symptomatic (broad-term) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to their baseline serology test status (i.e., seropositive or other, based on central lab test)	B
Proportion of subjects who subsequently have symptomatic (CDC definition) SARS-CoV-2 infection confirmed by RT-qPCR within the EAP according to baseline serology test status (i.e., seropositive or other, based on central lab test)	B
Number of weeks of symptomatic SARS-CoV-2 infection (strict-term) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Number of weeks of symptomatic SARS-CoV-2 infection (CDC definition) within 14 days of a positive RT-qPCR at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Time-weighted average change and percent change from baseline viral load (log10 copies/mL) in NP swab samples until the Day 22 visit according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Area under the curve (AUC) in viral load (log10 copies/mL) in NP swab samples from baseline to the first confirmed negative test according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Maximum SARS-CoV-2 RT-qPCR (log10 viral copies/mL) in NP swab samples during the EAP according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Number of medically attended visits in emergency rooms or urgent care centers related to RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Proportion of subjects requiring medically attended visits in emergency rooms or urgent care centers related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	B
Proportion of subjects hospitalized related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	B

Number of days of hospital and ICU stay in subjects hospitalized for a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Number of days missed for daily responsibilities (where applicable), including work (employed adults) or school (matriculating students), or family obligations/responsibilities (childcare or eldercare) due to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP, according to baseline serology test status (i.e., seropositive or other, based on central lab test)	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have asymptomatic infection during the EAP	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have symptomatic infection during the EAP	C
Maximum RT-qPCR viral load (log10 copies/mL) in NP swab samples during the EAP in subjects who have a medically attended visit related to a RT-qPCR confirmed SARS-CoV-2 infection at baseline or during the EAP	C

4.6. Safety Variables

4.6.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a “Preferred Term (PT)” and associated primary “System Organ Class (SOC)” according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.1). The severity of AEs (including test findings classified as AEs) and injection-site -related reactions will be graded by the investigator using the current version of the NCI–CTCAE v5.0 0. The NCI-CTCAE severity grading systems for anaphylaxis, allergic reaction, and injection site reaction are specifically in section 10.2.4 of the protocol.

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A serious adverse event is an adverse event (AE) that is classified as serious according to the criteria specified in the protocol.

For safety variables, the following observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent EAP (TEEAP) is defined as the day from first dose of study drug to 28 days after the last dose of study drug (Note: There is only one planned dose.)
- The treatment-emergent follow-up period (TEFUP) is defined from the day after the end of the TEEAP to the end of the Follow-up Period (i.e., last study visit).

Treatment-emergent adverse events (TEAEs) are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition.

Treatment-emergent adverse events (TEAEs) will be summarized for each of the following periods: treatment-emergent EAP, treatment-emergent follow-up period, and the study period (i.e. combination of the treatment-emergent EAP and follow-up periods). Adverse events that occur prior to treatment will be listed.

Laboratory results, physical examination, and vital signs are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to study discontinuation and/or fulfilling a seriousness criterion.

4.6.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol. In this study, AESI are listed below (as provided in the protocol), along with each AESI detailed definition:

- Grade 3 or greater injection site reactions or hypersensitivity reactions including but not limited to anaphylaxis, laryngeal/pharyngeal edema, severe bronchospasm, chest pain, seizure, or severe hypotension (eCRF specific tick box on the AE page)

4.6.3. Events Causing Death

Subject deaths are per the observation periods will be summarized as follows.

- Deaths during the TEEAP
- Deaths during the TEFUP
- Deaths during the overall study period

4.6.4. Laboratory Safety Variables

Samples for laboratory testing will be collected at visits according to the schedule of events tables in the protocol. Samples will be analyzed by a central laboratory. The clinical laboratory data consists of serum chemistry, hematology, urinalysis and other specified in section 9.2.3.2 of the protocol.

Clinical laboratory values will be converted and analyzed in both standard international (SI) units and US conventional units provided by the central laboratory. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) over time will be summarized, where the post-baseline visits will be assigned to the Global Analysis Windows (See Section 6.4).

Potentially clinically significant values (PCSV) ranges will be applied to the laboratory test values as applicable (see PCSV criteria in Appendix 10.3).

Vital Signs

Both actual test values and "change from baseline" (defined as the post-baseline value minus the baseline value) over time in vital signs parameters (e.g., weight (kg), height (cm), BMI (kg/m^2), temperature (^{0}C or ^{0}F), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg)) will be summarized as laboratory safety variables. Potentially clinically significant values (PCSV) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.3 for PCSV criteria).

4.6.5. Physical Examination Variables

Physical examination will be conducted as the protocol scheduled visits. If any abnormal findings during the screening period, they will be recorded in medical history eCRF form and AE eCRF form for any findings during post-screening period.

4.7. Pharmacokinetic Variables

The pharmacokinetic variables are the concentrations of REGN10933 and REGN10987 in serum and time when a sample was collected. The sampling time points for dense and sparse collection schedules are specified in the schedule of events tables in the protocol.

4.8. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, and time-point/visit. Serum samples for Immunogenicity will be collected at the clinic visits specified in the schedule of events tables in the protocol.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Baseline is defined as the last assessment obtained before the first dose of study drug.

Statistical hypotheses will be performed in seronegative subjects in Cohort A and Cohort B independently with separate type I error controls.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group and overall, for the study. These will be analyzed by cohort for both seronegative mFAS and SAF populations.

5.2. Medical History

Medical history will be summarized by SOC and PT and by treatment group and all groups combined for the seronegative mFAS populations defined in Section 3.1.

5.3. Prior/concomitant Medications or Procedures

All prior medications will be descriptively summarized by treatment group and overall, for the study, for subjects in SAF population.

Summaries will present subject counts (and percentages) for all prior medications, by decreasing frequency of the overall group incidence of ATC followed by ATC level 2, ATC level 4 and preferred term. For prior procedure, summaries will be by SOC and PT, sorted by decreasing frequency of SOC and PT based on the incidence in the overall group incidence. Subjects will be counted only once for each SOC and PT linked to the procedure.

All concomitant medications/procedures will be descriptively summarized by treatment group and observation period defined in Section 4.6.1, for subjects in SAF.

5.4. Prohibited Medications

Listing of prohibited medications described in Section 4.4 will be provided for subjects in SAF.

5.5. Subject Disposition

Subject study status will be summarized by treatment group and overall for the study.

The following will be provided:

- Number of screened subjects, defined as signed the ICF
- Number of randomized subjects
- Number of subjects randomized but who did not receive study treatment
- Number of subjects who discontinued the study, and the reasons for discontinuation

- A listing of subjects treated but not randomized, subjects randomized but not treated, and subjects randomized but not treated as randomized
- A listing of subjects prematurely discontinued from the study, along with reasons for discontinuation
- A summary of analysis sets including randomized subjects and randomized subjects by cohort, mFAS sets, SAF, PK, immunogenicity (ADA).

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Measurement of Compliance

Subject treatment compliance is not applicable for this study, since the study drug is administered once at the site and will be the same as treatment exposure.

5.6.2. Exposure to Investigational Product

The duration of study treatment will be defined as 28 days after the last dose for a subject in SAF.

5.7. Analyses of Efficacy Variables

The following null and alternate hypotheses will be tested for the primary and secondary endpoints unless otherwise specified:

H0: There is no treatment difference between REGN10933+REGN10987 and placebo

H1: There is a treatment difference between REGN10933+REGN10987 and placebo

5.7.1. Analysis of Primary Efficacy Variables

Cohort A

The Cohort A primary efficacy endpoint described in Section 4.5.1 will be analyzed in the seronegative mFAS-A population. All post-baseline efficacy assessments obtained in the EAP will be included for the primary analysis.

In order to account for the correlation among subjects within a household and control the associated type 1 error inflation, a generalized linear model will be used to estimate the odds ratio between the treatment groups by using the GEE approach (See Appendix 10.4 for an example of SAS procedure). This model estimates a single within-household correlation coefficient. The model will include the fixed category effects of treatment group (placebo versus REGN10933+REGN10987), region (US versus ex-US), and age (≥12 to <50, ≥50 years). The model will use a compound symmetry covariance matrix and estimate the odds ratio between the treatment groups and corresponding 95% CI and p-value.

If the GEE model fails to converge due to most households containing only a single study subject in seronegative mFAS-A or the percentage of households in Cohort A with only a single study subject is 70% or more, then a logistic regression model will be used with treatment, region, and age group as fixed effects. The threshold of 70% was based on simulations of within-household correlation which show the type I error rate is inflated and the power is decreased when the proportion of single-subject households is high (details provided in Section 6.6). If the logistic regression model does not converge, an exact logistic regression will be used. The estimates of odds ratio, the corresponding 95% CI and p-value will be provided from logistic regression (or exact logistic regression) for comparison of REGN10933+REGN10987 against placebo group.

In Cohort A, a subject will be considered having a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP if any of the post-baseline RT-qPCR results during the EAP are positive with at least one symptom within 14 days of a positive RT-qPCR result (Section 4.5).

Cohort B

The Cohort B primary efficacy endpoint described in Section 4.5.5 will be analyzed in the seronegative mFAS-B population. The same statistical methods as described for Cohort A will be used to obtain the estimate of odds ratio and p-value for comparison between the treatment groups.

In Cohort B, a subject will be considered having a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP if subjects have at least one symptom within 14 days of a positive RT-qPCR result at baseline or during the EAP.

Handling of Missing Central Lab SAR-CoV-2 RT-qPCR Data for Both Cohort A and Cohort B

Subjects with COVID-19 symptoms that are missing a central lab determined RT-qPCR test during the EAP (eg. are too sick to go to the study site) but have a positive SARS-COV-2 test from a local lab (eg. in the hospital) will be considered as having a symptomatic infection if any of the symptoms occurred within 14 days of the positive SARS-COV-2 test that was observed during the EAP.

The graphical display using Kaplan-Meier curve for the time to first symptom will also be provided.

5.7.1.1. Sensitivity Analyses

Robustness of the primary analyses results in Cohort A and Cohort B will be assessed through sensitivity analyses as follows:

Sensitivity analysis by excluding subjects who develop asymptomatic or symptomatic SARS-CoV-2 infection within 72 hours of the study drug administration

This analysis assesses for the sensitivity of the results to subjects who may have had undetected infections prior to dosing. That is, a subject had any onset of a positive RT-qPCR within 72 hours of the study drug administration will be excluded for this sensitivity analysis.

This sensitivity analysis will only be performed for Cohort A primary endpoint.

Sensitivity analysis by excluding subjects from non-good clinical practice (GCP) Compliant Site(s)

To access the impact of sites that had non-GCP compliance issues on the primary efficacy points, the primary analyses will be performed by excluding non-GCP compliant site(s).

This sensitivity analysis will be performed for both Cohort A and Cohort B primary endpoints.

5.7.1.2. Subgroup Analyses

To assess the homogeneity of the treatment effect across various subgroups, the primary analysis model with GEE approach will be applied to each subgroup if applicable; otherwise, the logistic regression model will be used. Odds ratio between the treatment groups and corresponding 95% CI will be provided, as well as the within-household correlation coefficient from GEE approach, within each subgroup.

The following subgroups of interest for Cohort A and Cohort B primary endpoints will be evaluated:

- Stratification age (years) group (≥12 to <18, ≥18 to <50, ≥50), and the additional age group: ≥12 to <18, and ≥18 years
- Sex
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other, where "Other" may include, for example, not reported, unknown, and multiracial, etc.) and an additional race group (White Hispanic or Latino, White not Hispanic or Latino, Black Hispanic or Latino, Back not Hispanic or Latino, and Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not reported or unknown)
- BMI (<30, ≥30)
- Number of study subjects in cohort B within a household (0, ≥1) (Cohort A only)
- Total household size including the household member(s) not participating this study (2, and >2)
- Region (US, ex-US)
- Baseline high risk factor (Yes versus No) (as defined in Section 4.1)
- Healthcare worker (Yes/No) per exposure risk factor eCRF
- High viral load (> 4 log 10 copies/ml) at baseline (Yes/No) (Cohort B only)

5.7.2. Adjustment for Multiple Comparison

The overall type I error will be controlled in each of seronegative mFAS-A and seronegative mFAS-B independently at 2-sided 5% significance level.

Seronegative mFAS-A Subjects

The overall type I error will be controlled for the primary hypothesis in Cohort A based on a 2-sided test at an alpha level of 0.05 as follows:

> H0: There is no treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP.

H1: There is a treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects with a symptomatic RT-qPCR confirmed SARS-CoV-2 infection during the EAP

If the primary efficacy endpoint in Cohort A is statistically significant, the alpha level of 0.05 will be released for the key secondary endpoints in Cohort A. The hierarchy testing sequence of key secondary endpoints is presented in the following table.

Table 2: Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-A

Key Secondary Efficacy Variables
Proportion of subjects with viral load >4 (log10 copies/mL) in NP swab samples during the EAP
Number of weeks of symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP
Number of weeks of high-viral load >4 (log10 copies/mL) in NP swab samples during the EAP
Number of weeks of RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
Proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP
Proportion of subjects in placebo group with a RT-qPCR confirmed SARS-CoV-2 infection during the EAP with an index case participating in study R10933-10987-COV-2067 (comparison of those whose index cases receive REGN10933+REGN10987 vs placebo in R1033-10987-COV-2067)

<u>Seronegative mFAS-B Subjects</u>

The overall type I error will be controlled for the primary hypothesis in Cohort B based on a 2-sided test at an alpha level of 0.05 as follows:

H0: There is no treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

H1: There is a treatment difference between REGN10933+REGN10987 and placebo in the proportion of subjects who subsequently develop signs and symptoms (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP

If statistical significance is established for the primary efficacy endpoint in cohort B, a hierarchical testing procedure will be applied to the key secondary endpoints in Cohort B at a 2-sided 0.05 significance level. The order of testing sequence for key secondary endpoints is presented in the following table.

Table 3: Hierarchy Testing Sequence of Key Secondary Efficacy Endpoints in Seronegative mFAS-B

Key Secondary Efficacy Variables
Number of weeks of symptomatic SARS-CoV-2 infection (broad-term) within 14 days of a positive RT-qPCR at baseline or during the EAP
Number of weeks of high viral load (log10 copies/mL) >4 in NP swab samples during the EAP

5.7.3. Analyses of Key Secondary Variables

For Cohort A, the key binary endpoint of the proportion of subjects who have a RT-qPCR confirmed SARS-CoV-2 infection (regardless of symptoms) during the EAP, the same statistical method used in the primary analysis will be applied. If a subject's overall infection status during the EAP cannot be determined due to missing RT-qPCR results, the following rules will be applied to impute the missing RT-qPCR data.

1. For subjects satisfying the criteria specified in the handling missing central lab SARS-CoV-2 RT-qPCR data of the analysis of primary efficacy variables, the corresponding visit(s) will be considered as having a positive RT-qPCR test.
2. After the first step above, each planned visit with missing RT-qPCR data will be imputed 100 times to generate 100 complete datasets based on the predicted probability using the fully conditional specification (FCS) (Van Buuren, S, 2005)[7] through the logistic regression. The logistic regression model includes the fixed effect factors of treatment group, region, age group, and RT-qPCR testing status at other analysis visits during the EAP. This imputation will repeat by iterating for each analysis visit with missing RT-qPCR testing status. Appendix 10.4 provides details on the use of FCS from the SAS MI procedure. These 100 complete datasets will be analyzed using the model specified above for the primary analysis. Results from 100 analyses will be combined using Rubin's formulae to obtain the final estimate of log(odds ratio), 95% CI and the associated p-value. The odds ratio and 95% CI will be derived by taking the exponential of these estimates.

For the key binary endpoint of the proportion of subjects with viral load >4 (log10 copies/mL), if NP swab viral load data is missing for a visit, it will not be imputed regardless of symptoms. Only non-missing available NP swab viral load data will be used for the analysis of this endpoint. Only subjects with at least one post-baseline viral load (log10 copies/mL) data in NP swab samples will be included in the analysis.

For Cohort A the key binary endpoint regarding the index case linkage to R10933-10987-COV-2067, the Fisher's exact test will be used.

For continuous key secondary endpoints in Cohort A and Cohort B (e.g., number of weeks of high viral load >4 (log10 copies/mL) in NP swab samples and number of weeks of symptomatic RT-qPCR-confirmed SARS-CoV-2 infection (broad-term) during the EAP, etc.), visits with missing viral load regardless of symptoms and visits with missing RT-qPCR that do not have any broad-term symptoms within 14 days will not be considered as meeting these endpoint criteria, respectively. For endpoints regarding viral load, only subjects with at least one post-baseline data will be included in the analysis. These endpoints will be analyzed by the non-parametric method, a stratified Wilcoxon rank sum test (Van Elteren Test) with the region and age group. Descriptive statistics will be provided for number (%) of subjects with each interval of duration in weeks (i.e., 0 week, > 0 to ≤ 1 week, > 1 to ≤2 weeks, etc.) within each treatment group. The total weeks of infection and normalized duration (e.g., average duration infection per 1000 subjects) per treatment group will also be reported.

5.7.4. Analyses of Other Secondary and Exploratory Efficacy Variables

Other secondary efficacy endpoints will be analyzed by type of endpoint defined in Sections 4.5.2 to 4.5.8 for all cohorts. The analysis methods for key secondary efficacy endpoints in both cohort A and cohort B will also be applied to exploratory endpoints in both cohort A and cohort B if appropriate. Otherwise, the primary approach to the data will be descriptive statistics. For the comprehensive evaluation of efficacy, nominal p-values may be reported. Raw data descriptive statistics will also be presented.

Other secondary efficacy and exploratory endpoints for cohort A1 and cohort B1 may also be analyzed by type of endpoint. If the sample size is sufficient, continuous variables will be summarized by the descriptive statistics (e.g., n, mean, SD, Q1, median, Q3, minimum and maximum, etc.). Binary variables will be summarized using the number and percentage of subjects in each treatment group. No statistical hypothesis testing will be performed for cohort A1 and cohort B1. This approach may also be applied to adolescent subjects.

Binary Endpoints

Binary endpoints in cohort A and cohort B will be analyzed by applying the same approach used for the primary efficacy endpoints.

For endpoints regarding viral loads, visits with missing viral load (log10 copies/mL) in NP swab samples will not be included in the analyses. For binary endpoints regarding the index case or household members linkage to R10933-10987-COV-2067 or subjects in cohort B, and endpoints regarding the medically attended visits, Fisher's exact test will be used. KM curves will be used to assess the exploratory endpoint of proportion of baseline-seronegative subjects who have a first RT-qPCR confirmed SARS-CoV-2 infection in the follow-up period.

Continuous Endpoints

The secondary and exploratory continuous efficacy endpoints such as TWA, AUC, and maximum viral load (log10 copies/mL) will be analyzed using the ANOVA including treatment group, region, and age group as fixed effects in the model. The continuous endpoints regarding change from baseline in cohort B (e.g., TWA of change/percent change from baseline) will be analyzed using the ANCOVA model with treatment group, region, and age group as fixed effects, and the relevant baseline values as covariate as well as treatment-by-covariate interaction. The REGN10933+REGN10987 group will be compared to the placebo group and corresponding least square of mean difference, standard error (SE) and 95% confidence interval will be provided. For other endpoints with non-normal/skewed distribution (e.g. number of days of symptoms (strict-term, and CDC definition, etc.)), Van Elteren test will be used.

5.7.5. Interim Analysis

No interim analysis will be conducted for this study.

5.8. Analysis of Safety Data

The analysis of safety and tolerability will be performed in SAF, as defined in Section 3.2. For each cohort, the safety analysis will also be performed by subject baseline serology status and age group (≥ 12 to <18 years and ≥18), respectively.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, and vital signs).

Thresholds for PCSV in laboratory variables, and vital signs are defined in Appendix 10.3.

The summary of AE results will be presented for each treatment group for each of three TEAE periods: treatment-emergent EAP (TEEAP), treatment-emergent follow-up period (TEFUP), and overall study period (i.e., combined across the TEEAP and TEFUP), and by study cohort. For laboratory and vital sign results they will be presented for each treatment group for each of three periods: EAP, follow-up, and overall study period.

General common rules

All safety analyses will be performed, unless otherwise specified, using the following common rules:

- Safety data in subjects who do not belong to the safety analysis set (i.e., exposed but not randomized) will be listed separately.
- PCSV values are thosevalues considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSV criteria described in Appendix 10.3). Considering that the threshold defined in the PCSV list for monocytes and basophils can be below the ULN, the following PCSV criterion will be used for the PCSV analysis of monocytes and basophils:
  - PCSV criterion for monocytes: >0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L).
  - PCSV criterion for basophils: >0.1 Giga/L or >ULN (if ULN ≥0.1 Giga/L).
- PCSV criteria will determine which subjects had at least 1 PCSV during the respective TEAE periods, taking into account all evaluations including unscheduled or repeated evaluations.
- The treatment-emergent PCSV denominator by treatment group for a given parameter will be based on the number of subjects assessed for that given parameter at least once during the respective TEAE periods.

- All unscheduled measurements will be assigned to Global Analysis Windows defined in Table 5 of Section 6.4 in order to provide an assessment for the screening/baseline visit through follow-up visit time points.
- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize observed values and change from baseline values by visit.

5.8.1. Adverse Events

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). The preferred term (PT), and the primary system organ class (SOC) will be listed.

The number and percentage of subjects with TEAEs will be summarized by treatment group. Summaries will include:

- Overview of TEAEs, i.e., overall number (%) of subjects with any TEAE, Serious TEAE, TEAE leading to death, TEAE leading to study drug withdrawn, or subjects with any COVID-19 TEAE or asymptomatic COVID-19 TEAE
- Overview of non-COVID TEAEs (excluding COVID-19 and asymptomatic COVID-19), i.e., overall number (%) of subjects with any TEAE, Serious TEAE, TEAE leading to death, or TEAE leading to study drug withdrawn
- Overview of AESI, i.e., overall number (%) of subjects with any AESI, grade 3 or greater injection site reactions, grade 3 or greater hypersensitivity reactions, AESI leading to death, or AESI leading to study drug withdrawn)
- TEAEs by primary SOC and PT
- Number of subjects experiencing common TEAE(s) by primary SOC and PT (PT incidence≥5% in any treatment group)
- TEAEs by severity (according to the grading scale outlined in section 10.2.4 of the protocol), presented by primary SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by primary SOC and PT
- Treatment-emergent SAEs by primary SOC and PT
- Treatment-emergent AESIs by primary SOC and PT
- TEAEs leading to study drug withdrawn by primary SOC and PT
- Treatment-emergent AESIs leading to study drug withdrawn by primary SOC and PT
- Treatment-emergent AESIs by severity, presented by primary SOC and PT
- Number of subjects who died during TEEAP, TEFUP, and the study period, respectively, and reason for death
- TEAEs leading to death (death as an outcome on the AE CRF page, as reported by the Investigator) by SOC and PT

- AESIs leading to death (death as an outcome on the AE CRF page, as reported by the Investigator) by SOC and PT.

In addition, the number (%) of subjects with any post-baseline fever reported from the fever assessment eCRF, any subject self-recorded symptoms assessment collected in the COVID-19 symptoms assessment eCRF will be summarized by treatment group. The descriptive statistics of the duration (days) of each COVID-19 symptom will also be presented. Subject listing of COVID-19 symptoms including the details such as the start date, end date, and duration of each symptom will be provided. In addition, subject listing of SAEs, AESI, TEAEs related to study drug, and TEAEs leading to study drug withdrawn will also be presented.

5.8.2. Clinical Laboratory Measurements

For the respective EAP, FUP, and overall study period, clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit by treatment group.

Individual subject laboratory parameter measurements will be additionally evaluated by PCSV criteria (See Appendix 10.3), specifically identifying subjects with at least one post-baseline measurement that meets the PCSV criteria. These laboratory parameters will be presented by the biological functions. The incidence of PCSVs at any time during the respective treatment-emergent periods (EAP and FUP) will be summarized regardless of the baseline level, and again according to the following baseline categories:

- Normal (according to PCSV criterion/criteria)/missing
- Abnormal according to PCSV criterion or criteria

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Subject listings of laboratory measurements that meet PCSV criteria will be provided for the report appendix.

A listing of all women of childbearing potential with a confirmed serum pregnancy test during the study will be provided.

5.8.3. Analysis of Vital Signs

For the respective EAP, FUP, and overall study period, the vital sign actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit will be summarized by treatment group.

Individual subject laboratory parameter measurements will be additionally evaluated by PCSV criteria (See Appendix 10.3), specifically identifying subjects with at least one post-baseline measurement that meets the PCSV criteria.

Subject listings of vital sign measurements that meet PCSV criteria will be provided for the report appendix.

5.8.4. Analysis of Other Safety Variables - Abnormal Findings during SARS-CoV-2 Infection-related Medically Attended Visits

For subjects who become SARS-CoV-2 positive and require medically attended visits to the emergency department (ED), urgent care center (UCC), or hospitalization starting from the timepoint of SARS-CoV-2 RT-qPCR positive and through the end of the study, will have the following parameters or occurrences (worst or most abnormal finding) during the medically attended visit/stay collected (eCRF).

- Nature of visit (ED, UCC, hospital stay)
- Abnormal vital signs: respiratory rate ≥30 per minute, heart rate ≥125 per minute, peripheral capillary oxygen saturation (SpO2) ≤93% on room air at sea level, or oxygen partial pressure (PaO2)/fractional inspired oxygen (FiO2) <300 mm Hg)
- Respiratory failure: needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, extracorporeal membrane oxygenation (ECMO)
- Evidence of shock: systolic blood pressure (SBP) <90 mm Hg, diastolic blood pressure (DBP) <60 mm Hg or requiring vasopressors (*Note: these limits for abnormal vital signs are for adult and adolescent subjects.)*
- Multiorgan dysfunction: Significant acute renal, hepatic, or neurologic dysfunction
- Multisystem inflammatory syndrome in children (MIS-C). (Note: for pediatric subjects <12 years only.)
- Admission to an ICU

Number and percentage of subjects who presented at least one of abnormal findings and then by each of these 5 abnormal findings will be provided by treatment group and TEAE period (TEEAP, TEFUP, and overall study period). Within each abnormal findings, number and percentages of subjects will also be reported for each observed criterion.

A listing of subjects who have any of these abnormal findings with any SARS-CoV-2 infection-related medically-attended visit will be provided including the corresponding study period information.

5.9. Analysis of Pharmacokinetic Data

5.9.1. Analysis of drug concentration data

Concentrations of REGN10933 and REGN10987 over time will be summarized by descriptive statistics for each cohort. No formal statistical hypothesis testing will be performed.

Dense PK sentinel cohort

The PK parameters to be determined after the first dose for REGN10933 and REGN10987 may include, but are not limited to:

- C_{max}
- C_{max}/Dose

- t_{max}
- t_{last}
- C_{last}
- AUC_{inf}
- AUC_{inf}/Dose
- $t_{1/2}$
- C_{28} (concentration in serum 28 days after dosing)

Selected PK parameters will be summarized by descriptive statistics for each cohort. Results from two different cohorts may be combined if appropriate.

Sparse PK

Concentrations of REGN10933 and REGN10987 in serum over time will be summarized by descriptive statistics for each cohort. No formal statistical hypothesis testing will be performed.

5.10. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 4.8 will be summarized using descriptive statistics.

Immunogenicity will be characterized by ADA responses and titers observed in subjects in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA response categories:

- ADA Negative, defined as ADA negative response in the ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as an ADA positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.

- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

Titer categories (Maximum titer values)

  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative subjects (pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive subjects by treatment groups and ADA titer categories and at the
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive subjects
  - Number (n) and percent (%) of transient treatment-emergent ADA positive subjects
- Number (n) and percent (%) of treatment-boosted ADA positive subjects by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for subjects with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.10.1. Analysis of Neutralizing Antibody (NAb) Data

The absolute occurrence (n) and percent of subjects (%) with NAb status in the NAb analysis set will be provided by treatment groups.

5.11. Association of Immunogenicity with Exposure, Safety and Efficacy

5.11.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to will be explored by treatment groups. Plots of drug concentration time profiles may be provided to examine the potential impact of ADA response status, titer, and NAb on these profiles.

5.11.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])

- Anaphylaxis reaction (SMQ: Anaphylaxis [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA positive subjects: subjects with treatment-emergent or treatment-boosted response.
- ADA negative subjects: subjects with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- Subjects with persistent treatment-emergent ADA response
- NAb positive subjects: ADA positive subjects who were positive in the NAb assay at any time point analyzed.
- Maximum post-baseline titer in treatment-emergent or treatment-boosted ADA positive subjects:
  - Low (titer <1,000)
  - Moderate (1,000 ≤ titer ≤10,000)
  - High (titer >10,000)

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available measurement taken prior to the administration of study drug.

6.2. Data Handling Convention for Efficacy Variables

Rules for handling missing RT-qPCR test results for primary and secondary efficacy variables are described in Section 5.7.1.

6.3. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Date and Time of Study Treatment Injection

Since the study drug is administered at the site, the date and time of study drug administration are filled in eCRF. No missing data is expected. The information is filled in eCRF.

Adverse Event

If the severity of a TEAE is missing, it will be classified as "severe" or "Grade 3" in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to study drug.

When the partial AE date/time information does not indicate that the AE started prior to study treatment or after the TEAE period, the AE will be classified as treatment-emergent.

Medication/Procedure

If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly or stopped prior to the first study treatment administration, it will be considered as concomitant medication/procedure by imputing the start date on the date of first study treatment administration.

Potentially Clinically Significant Value (PCSV)

If a subject has a missing baseline value, this subject will be grouped in the category "normal/missing at baseline."

For PCSVs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSV will be based only on the second condition.

For a PCSV defined on a threshold and/or a normal range, this PCSV will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSV is >0.5 giga/L or >ULN if ULN ≥0.5 giga/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSVs.

6.4. Windows for Analysis Time Points

Data analyzed by-visit-analysis will be summarized by the scheduled visit described in protocol section 9.1 Schedule of Events. Below are the definitions for the visit windows programmatically imposed on all available measures from unscheduled visits collected over the course of the study including early termination visit and end of study visit. No analysis visit windows will be applied for the study scheduled visits nor for drug concentration and immunogenicity data.

The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Below are the relevant definitions for the analysis visit windows:

1. The first study treatment occurs on Study Day 1.
2. Study day is defined as the number of days since the first study treatment administration+1.
3. Since the protocol specifies that measurements be collected before study treatment is administered on a given day, it is appropriate that baseline include Day 1.
4. For randomized but not treated subjects, Day 1 is the day of randomization.

Table 4: Efficacy Analysis Windows for Unscheduled Visits with RT-qPCR or Viral Load Results

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Week 1	8	[2, 11]
Week 2	15	[12, 18]
Week 3	22	[19, 25]
Week 4	29	[26, 32]
Week 5	36	[33, 39]
Week 6	43	[40, 46]
…	…	…
Week x	29+7x	[26+7(x-4), 32+7(x-4)]

If a subject has multiple efficacy assessment visits within an analysis visit window, the one with worst result (e.g., the positive test result will be used for analysis if one record is positive and the other one is negative; the highest viral load result will be used if multiple viral load results are in the same analysis window.) will be selected. If the test results are all negative, the value of the latter visit will be used. If there are multiple positive RT-qPCR results within an analysis window, the record with the highest quantitative result will be used.

Table 5: Global Analysis Windows for Data Other Than RT-qPCR Test

Visit Label	Targeted Study Day	Analysis Window in Study Day
Baseline	1	≤ 1
Day 2	2	[2, 2]
Day 4	4	[3, 4]
Week 1	8	[5, 11]
Week 2	15	[12, 18]
Week 3	22	[19, 25]
Week 4	29	[26, 42]
Week 8	57	[43, 70]
Week 12	85	[71, 98]
Week 16	113	[99, 126]
Week 20	141	[127, 154]
Week 24	169	[155, 182]
Week 28	197	[183, 210]
Week 32	225	>=211

Unscheduled Assessments

For efficacy, safety laboratory data, and vital signs, unscheduled visit measurements may be used to provide a measurement for a time point, including baseline, if appropriate according to their definitions. The measurements may also be used to determine abnormal values, AESIs, and PCSVs.

6.5. Pooling of Centers for Statistical Analyses

Currently, the randomization is stratified by site. Since a potential differential treatment effect among countries may exist, region variable as a fixed effect factor will be included in the statistical analysis model. A subgroup analysis regarding region will also be performed for the primary efficacy endpoint. Results will also be summarized descriptively by country.

6.6. Statistical Technical Issues

To consider the potential impact that not all of study subjects come from a household with more than one member participating this trial, a simulation has been conducted to explore the potential impact to the type I error rate and power by the percent of households with a single study subject only.

This simulation is based on the same sample size of 1248 (See Table 1 in Section 2.2.1) assuming the attack rates are 10% and 5% in placebo and REGN10933+REGN10987 treatment group, respectively. The correlated Bernoulli response data (e.g. 1=infected vs 0=not infected) within a household was generated by using Gaussian multivariate cumulative distribution function proposed by Emrich and Piedmonte (1991). For example, the table below exhibits the correlation between the bivariate normal data with correlation ρ used to generate the Bernoulli correlated data and the corresponding Bernoulli correlation γ in the cases where the attack rates are both 10% (e.g., $p_1 = p_2 = 0.1$ under the null hypothesis), and 10% and 5% (e.g., $p_1 = 0.1, p_2$ =0.05 under the alternative hypothesis).

$p_1 = p_2 = 0.1$	
ρ Normal	γ Bernoulli
0.1	0.03706
0.2	0.07996
0.3	0.12907
0.4	0.18504
0.5	0.24891
0.6	0.32242
0.7	0.40866
0.8	0.51381
0.9	0.65405

$p_1 = 0.1, p_2 = 0.05$	
ρ Normal	γ Bernoulli
0.1	0.03065
0.2	0.06748
0.3	0.11089
0.4	0.16150
0.5	0.22020
0.6	0.28834
0.7	0.36813
0.8	0.46328
0.9	0.58016

Given the percent of subjects from households with single study subject (HHS), the rest of household size was randomly generated by using a truncated Poisson ($l = 4$) (i.e., resampling if ≤1). The simulation is repeatedly 2000 times by different HHS to compare the power between GEE model and logistic regression model based on boundary p-value=0.044 after 2 planned interim analyses.

Summary of power and type I error rate between the GEE model and logistic regression model by different HHS, considering the extreme high correlated data. The power is based on the testing p-value compared to the boundary p-value of 0.044 after 2 interim analyses at 50% and 75% information fraction for the final analysis.

Comparisons of Power

$\gamma = 0.58$ ($p_1 = 0.1, p_2 = 0.05$)		
HHS(%)	power-GEE	power-Logistic
10	0.9920	0.9035
20	0.9905	0.9040
30	0.9855	0.9140

Comparisons of Type I Error

$\gamma = 0.65$ ($p_1 = 0.1, p_2 = 0.1$)		
HHS(%)	α-GEE	α -Logistic
10	0.0480	0.0435
20	0.0490	0.0440
30	0.0495	0.0475

40	0.9590	0.8980
50	0.9245	0.9075
60	0.9035	0.9085
70	0.8640	0.9175
80	0.8460	0.9155

40	0.0510	0.0445
50	0.0410	0.0360
60	0.0600	0.0490
70	0.0575	0.0390
80	0.0735	0.0370

Based on the potential inflation of type I error (α) and decreasing power as HHS over 50%, conservatively the percent of households with a single study subject could be higher than 70%. Thus, if this situation occurs, the logistic regression will be used instead of using GEE approach.

7. TIMING OF STATISTICAL ANALYSES

There are multiple steps of analyses planned for this study.

- An administrative descriptive analysis based on approximately first 554 randomized Cohort A subjects has been conducted. No formal statistical hypothesis testing will be performed. The individuals who have the subject treatment information will be described in the communication plan.
- The first step analysis: The database lock will occur when all Cohort A and Cohort B subjects complete the EAP and all their data during the EAP have been collected and validated. The individual treatment codes will be unblinded and final analyses of the primary and some secondary efficacy endpoints of cohort A and Cohort B will be conducted. The subjects who are included in the administrative analysis will not be included in the first step efficacy analysis. Also, subjects who are randomized after January 28^{th} (approximately 269) will not be included in this analysis.

  Note: The results of primary and some secondary efficacy endpoints in the first step analysis maybe used for a submission dossier to health authorities.
- The second step analysis (final analysis): The database lock will occur after the last subject completes the study. All treated subjects including 554 subjects in the administrative assessment, subjects in the first step analysis, and those subjects (~269) who were randomized after 28 January, 2021, will be included in the safety analysis. The second-step analysis for efficacy will include all subjects except those subjects who were included in the administrative assessment.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher, and R 3.5.3 or higher.

9. REFERENCES

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10. APPENDIX

10.1. Summary of Statistical Analyses

Primary Efficacy Analysis:

Endpoint	Analysis Population	Estimand	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) during the EAP	Seronegative mFAS-A	A broad-term symptom occurring within a 14-days window of any positive RT-qPCR during the EAP regardless of adherence to study treatment will be included for the primary analysis.	A generalized linear model with the generalized estimation equation (GEE) approach or logistic regression If percent of households with single study subject greater than or equal to 70%. Missing RT-qPCR will be imputed as positive RT-qPCR if a subject with COVID-19 signs and symptoms (broad-term) occurring within a 14-day window of a visit with missing RT-qPCR data.	Yes	Yes	1. Excluding those subjects who develop asymptomatic or symptomatic SARS-CoV-2 infection within 72 hours of the study drug administration 2. Exclude subjects from non-GCP compliance sites
Proportion of subjects who have a symptomatic RT-qPCR confirmed SARS-CoV-2 infection (broad-term) at baseline or during the EAP	Seronegative mFAS-B	Same as above including a positive RT-qPCR at baseline	Same as above including a positive RT-qPCR at baseline	Yes	No	1. Exclude subjects from non-GCP compliance sites

10.2. Schedule of Events

Table 6: Schedule of Events Cohorts A and B ([Adult / Adolescent Subjects], RT-qPCR-Negative and Positive)

Visit	Screening / Baseline[1]	Additional Safety (Sentinel Only)[2]				Efficacy Assessment Period (EAP)[3]				Follow-up Period							ET	Unscheduled Visit[4]
Visit Location Site (S), Phone (P)[5]	**S**	**S**	**S**	**P**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**		
Visit Number	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS**		
Day	1	1	2	3	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)						±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Screening/Baseline:																		
Inclusion/exclusion	X																	
Informed consent (adult subject or parent/guardian)/pediatric assent (adolescent subject)	X																	
[redacted]	X																	
Medical history	X																	
Demographics and risk factors for SARS-CoV-2 infection	X																	
Household assessment	X[16]								X									
Appropriate sample, diagnostic assay for SARS-CoV-2 (local lab)	X[7]																	
Randomization	X																	
Treatment:																		
Study drug administration	X[8]																	
Efficacy (Virology):																		
NP swab, SARS-CoV-2 RT-qPCR (central lab)[7,17]	X[8]					X	X	X	X	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X[3,4,9]	X	X
Efficacy (Subject-Reported) only for RT-qPCR positive subjects:																		
Assessment of ED, UCC, hospital visits[18]						X	X	X	X	X	X	X	X	X	X	X		
Absenteeism assessment[18]						X	X	X	X							X		
Safety:																		
Vital signs	X[2,11]	X[2]							X							X		X
Targeted PE[11]	X		X		X				X							X		X
Adverse events[15,19]	X	X[2]	X[2]	X[2]	X[2,10]	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds, Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test for WOCBP (dipstick, local lab)[12]	X															X		X
Laboratory Testing[13]:																		
Clinical Laboratory, Hematology, Blood Chemistry, Urinalysis	Refer to Table 7																	
Pharmacokinetics and Immunogencity[13]:																		
Drug concentration	Refer to Table 7																	
Anti-drug antibodies (ADA)																		

Biomarkers:																		
Serum for serology (central lab)[14]	X								X	X						X		
Research plasma	X								X[20]	X[20]						X[20]		
Research serum	X								X[20]	X[20]						X[20]		
[redacted]																		
[redacted]	X								X[20]	X[20]						X[20]		
[redacted]	X																	

EAP, Efficacy assessment period; EOS, end of study; ED, emergency departments; ET, Early termination; UCC, urgent care centers; PE, physical exam; [redacted] RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

10.2.1. Schedule of Events Table 6 (Cohorts A and B [Adult / Adolescent Subjects], RT-qPCR-Negative and Positive) Footnotes

1. The screening visit and baseline visit should both occur on the same day. If needed, a remote visit may occur to sign the ICF and collect medical history and concomitant medication use, on the day prior to, but within 24 hours of study drug administration, so that the in-person screening and randomization visit may be abbreviated, due to COVID-19 considerations. Study drug administration must occur within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.

2. The sentinel group (see Section 6.1.1 of the protocol) had additional safety monitoring on day 1 and through day 4.

   Vital signs: On day 1, vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) will be measured at predose, approximately every 30 minutes during the first 2 hours after dose, at hour 3, and at hour 4 before dismissal.

   Adverse Events (injection site reactions and hypersensitivity): after the administration of the first dose of study drug, subjects will be monitored on site for a minimum of 4 hours and then by daily visits to the study site or phone calls for the first 4 days (96 hours), particularly focusing on the assessment of injection site reactions and hypersensitivity after study drug administration.

3. Subjects who have a positive RT-PCR result during screening, or who have a positive RT-qPCR result any time after screening, will have the additional assessments done as indicated (**RT-qPCR positive subjects only**). A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

   For subjects who become RT-qPCR positive after screening, the visit schedule will proceed as follows: (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

4. Unscheduled visits: If, at any time after randomization until end of study, a subject develops fever, an acute respiratory illness or other symptoms they may feel could be related to COVID-19 or is hospitalized for suspected COVID-19, the subject or parent/guardian (adolescent pediatric subject) should alert the investigator or designee immediately who will assess the subject's symptoms and condition (can be performed by phone contact, telemedicine, online meeting, home health care, etc) to decide if the subject should have an unscheduled visit for collection of NP swab sample for RT-qPCR testing. The subject or parent/guardian (adolescent pediatric subject) may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1 of the protocol). The investigator or designee should query the subject about AEs in general and AEs consistent of COVID-19 and record the information on CRF (see detailed description of the procedure in Section 9.2.2.2 of the protocol).

   (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

5. Visit may occur by phone or electronic means

[redacted]

7. Sample for diagnostic assay for SARS-CoV-2 (local lab) (see Section 9.1.2 of the protocol) and RT-qPCR (NP swab; central lab) should be collected before administration of study drug. Samples for RT-qPCR (NP swab) will be collected by swabbing through both nostrils (see Section 9.2.2.1 of the protocol). The remnant samples may additionally be used for exploratory viral RNA sequencing and viral infectivity analyses. The requirement for a local diagnostic assay for SARS-CoV-2 may be waived if the results are not expected to be available in a timely manner for randomization.

8. Study drug should be administered after all biological samples at screening/baseline have been collected.

9. Subjects who are RT-qPCR positive at the end of the EAP will continue to have samples collected weekly (NP swab; central lab) for RT-qPCR. Subjects will continue assessments/sample collections until 2 negative RT-qPCR test results have been

obtained ≥24 hours apart (all samples must be negative). Subjects who are RT-qPCR negative at the end of the EAP will have samples collected only if they become symptomatic with COVID-19 in the follow-up period.

10. For subjects who are not in the sentinel group (subset 1; completed), vital signs will be monitored on site as follows: Safety group (subset 2; completed): at baseline predose and then every hour for 2 hours after study drug administration and a phone call on day 4 to assess AEs, specifically injection site reactions and hypersensitivity; all other subjects (subset 3): at baseline and 1 hour after study drug administration. All subjects will be advised to call the site if signs/symptoms of injection site or hypersensitivity reactions occur. If the subject experiences a true medical emergency, they should visit their local hospital ED and contact the site personnel later.
11. The investigator may perform a targeted physical exam, request an exam and/or vital signs at any time. These assessments can be performed using a clinic visit or a remote visit with the investigator or sub-investigator, or designee (ie, nurse practitioner in countries where allowed by local law).
12. For <u>all</u> women of childbearing potential (WOCBP) and girls at or beyond menarche, except subjects with a confirmed pregnancy. If the local urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation.
13. Samples for drug concentration and, immunogenicity, and laboratory testing will be collected based on the subject subset designation as indicated in Table 7.
14. The serology test results will not be communicated to the sites. The sponsor's blinded study team will not have access to post-baseline results associated with subject identification until after the database is locked.
15. During each scheduled or unscheduled visit/contact, the investigator or designee will query subject about AEs in general (see Section 10.1.1 of the protocol) and evaluate if the AEs are associated with SARS-CoV-2 infection, including fever (see Section 9.2.2.2 of the protocol). The investigator should recommend that subjects (themselves or by their parent/guardian) measure their temperature daily during EAP, approximately at the same time, and also every time when the subject feels feverish, chills, or sick. Subjects with symptomatic SARS-CoV-2 infection should be queried on their symptoms weekly until symptoms resolve, even during follow-up period, then follow the regular schedule.
16. The information for the household assessment, including household members who receive an EUA approved monoclonal antibody treatment for COVID-19 or household members participating in the R10933-10987-COV-2067 study, should preferably be collected at the baseline visit. There will be a follow-up assessment at day 29.
17. All subjects will have a weekly NP swab sample collected during the EAP. Only subjects who are RT-qPCR positive will continue to have weekly NP swab samples collected during the follow-up period until 2 consecutive negative (≥24 hr) RT-qPCR results or the end of study visit.

18. Only for RT-qPCR positive subjects (cohort A and cohort B): Complete assessments from the time the subject first becomes RT-qPCR positive or from the time they develop symptoms suspected to be COVID-19 (later confirmed by RT-qPCR positive results) until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or until the end of study visit.
19. All subjects or parent/guardians of adolescent pediatric subjects will complete the TEAE assessment weekly during the EAP. Subjects who are RT-qPCR negative will complete the TEAE assessment monthly during the follow-up period. Subjects who have symptomatic SARS-CoV-2 infection will complete the TEAE assessment weekly during the follow-up period until the COVID-19 related symptoms resolve after which the subject will complete the TEAE assessment monthly until the end of study visit.
20. Samples will be collected only from RT-qPCR positive subjects (cohort A and cohort B) from the time the subject first becomes RT-qPCR positive until the end of study. Note: this includes subjects who have returned to RT-qPCR negative by this visit.

Table 7: Schedule of Events: Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentration, Immunogenicity, and Laboratory Testing

Samples for drug concentration (dense PK, sparse PK), immunogenicity assessment (ADA), and clinical laboratory testing (hematology, blood chemistry, and urinalysis) will be collected based on subset designation using subject number (assigned by IWRS):

- Sentinel group (Subset 1; completed): First 30 subjects
- Safety group (Subset 2; completed): 31st to 400th subject

All other subjects (Subset 3): 401st to last subject

Visit	Screening / Baseline[1]	Sentinel Group Only		Efficacy Assessment Period (EAP)				Follow-up Period							ET Visit[5]	Unscheduled Visit
Site (S)	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**			
Visit Number	**1**	**2**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS 15**		
Day	1	2	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)				±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Sentinel Group (Subset 1)																
Dense PK[2]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Blood chemistry[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Urinalysis[4]	X[1]	X	X				X	X	X	X	X	X	X	X	X	
Safety group (Subset 2)																
Sparse PK[2]	X[1]						X	X		X		X		X	X	X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]						X	X	X	X	X	X	X	X	X	
Blood chemistry[4]	X[1]						X	X	X	X	X	X	X	X	X	
Urinalysis[4]	X[1]						X	X	X	X	X	X	X	X	X	
All other subjects (Subset 3)																
PK[2]																X[6,7]
ADA[2,3]	X[1]						X			X				X	X	X[6,7]
Hematology[4]	X[1]						X									
Blood chemistry[4]	X[1]						X									
Urinalysis[4]	X[1]						X									

ADA, anti-drug antibodies; EAP, Efficacy assessment period; EOS, end of study; ET, Early termination; PK, Pharmacokinetics

10.2.2. Schedule of Events Table 4: All Cohorts A and B (Adult / Adolescent Subjects) for Drug Concentrations, Immunogenicity, and Laboratory Testing

1. Samples should be collected before the administration of study drug. Administration of study drug must be performed on the on same day as sample collection.
2. Actual dosing time and dense PK, sparse PK, and ADA sample collection times will be recorded.
3. At the screening/baseline visit, the window for baseline pre-dose ADA sample collection is as close to administration of study drug as is reasonable. Actual dosing times and ADA sample collection times will be recorded.
4. Whole blood samples for hematology and blood chemistry and urine samples for urinalysis will be analyzed at central lab.
5. Subjects who prematurely discontinue the study should have sample collection listed in the ET visit before exiting the study.
6. A PK serum sample and an ADA serum sample will be collected as soon as possible or within 7 days of receiving the first positive SARS-CoV-2 RT-qPCR result for cohort A subjects. The ADA serum samples may be analyzed for ADA and NAb, if feasible.
7. A PK serum sample and an ADA serum sample will be collected as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all subjects.

Table 8: Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive)

Visit	Screening / Baseline[1]	Additional Safety (Sentinel Only)[2]				Efficacy Assessment Period (EAP)[3]				Follow-up Period							ET	Unscheduled Visit[4]
Visit Location Site (S), Phone (P)[5]	**S**	**S**	**S**	**P[5]**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**		
Visit Number	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS**		
Day	1	1	2	3	4	8	15	22	29	57	85	113	141	169	197	225		
Week	0	0	0	0	0	1	2	3	4	8	12	16	20	24	28	32		
Window (day)						±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Screening/Baseline:																		
Inclusion/exclusion	X																	
Informed consent (parent/guardian)/pediatric assent (subject)	X																	
[redacted]	X																	
Medical history	X																	
Demographics and risk factors for SARS-CoV-2 infection	X																	
Household assessment	X[15]								X									
Appropriate sample, diagnostic assay for SARS-CoV-2 (local lab)	X[6]																	
Randomization	X																	
Treatment:																		
Study drug administration	X[7]																	
Efficacy (Virology):																		
NP swab, SARS-CoV-2 RT-qPCR (central lab)[6,16]	X[7]					X	X	X	X	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X[3,4,8]	X	X
Efficacy (Subject-Reported) only for RT-qPCR positive subjects:																		
Assessment of ED, UCC, hospital visits[17]						X	X	X	X	X	X	X	X	X	X	X		
Absenteeism assessment[17]						X	X	X	X							X		
Safety:																		
Vital signs	X[2,10]	X[2]							X							X		X
Targeted PE[10]	X		X		X				X							X		X
Adverse events[14,18]	X[9]	X[2]	X[2]	X[2]	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Meds, Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test for WOCBP (dipstick, local lab)[11]	X															X	X	
Laboratory Testing[12]:																		
Clinical Laboratory, Hematology, Blood Chemistry	Refer to Table 9																	
Pharmacokinetics and Immunogencity[12]:																		
Drug concentration / Anti-drug antibodies (ADA)	Refer to Table 9																	
Biomarkers:																		
Serum for serology (central lab)[12,13]	Refer to Table 9																	
[redacted]																		
[redacted]	Refer to Table 9																	
[redacted]	Refer to Table 9																	

EAP, Efficacy assessment period; EOS, end of study; ED, emergency departments; ET, Early termination; UCC, urgent care centers; PE, physical exam; RT-PCR, reverse transcription polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WOCBP, women of childbearing potential.

10.2.3. Schedule of Events Table 5 Cohorts A1 and B1 (Pediatric Subjects [<12 years], RT-qPCR-Negative and Positive) Footnotes

1. The screening visit and baseline visit should both occur on the same day. If needed, a remote visit may occur to sign the ICF and collect medical history and concomitant medication use, on the day prior to, but within 24 hours of study drug administration, so that the in-person screening and randomization visit may be abbreviated, due to COVID-19 considerations. Study drug administration must occur within 96 hours of collection of the index cases' positive SARS-CoV-2 diagnostic test sample.
2. The pediatric sentinel group (subset 4) (see Section 6.1.2 of the protocol) will have additional safety monitoring on day 1 and through day 4.

   Vital signs: On day 1, vital signs (pulse rate, respiratory rate, body temperature and blood pressure [if feasible, according to the child's age]) will be measured at predose, approximately every 30 minutes during the first 2 hours after dose before dismissal.

   Adverse Events (injection site reactions and hypersensitivity): after the administration of the first dose of study drug, subjects will be monitored on site for a minimum of 2 hours and then by daily visits to the study site or phone calls for the first 4 days (96 hours), particularly focusing on the assessment of injection site reactions and hypersensitivity after study drug administration.
3. Pediatric subjects who have a positive RT-PCR result during screening, or who have a positive RT-qPCR result any time after screening, will have the additional assessments done as indicated (**RT-qPCR positive pediatric subjects only**). A PK sample and an ADA sample will be collected (1) as soon as possible or within 7 days of receiving first positive SARS-CoV-2 RT-qPCR result for cohort A1 pediatric subjects and (2) as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all pediatric subjects.

   For pediatric subjects who become RT-qPCR positive after screening, the visit schedule will proceed as follows: (a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.
4. Unscheduled visits: If, at any time after randomization until end of study, a pediatric subject develops fever, an acute respiratory illness or other symptoms they may feel could be related to COVID-19 or is hospitalized for suspected COVID-19, the pediatric

subject and/or parent/guardian should alert the investigator or designee immediately who will assess the subject's symptoms and condition (can be performed by phone contact, telemedicine, online meeting, home health care, etc) to decide if the pediatric subject should have an unscheduled visit for collection of NP swab sample for RT-qPCR testing. The pediatric subject and/or parent/guardian may also be asked to provide blood samples if it corresponds to a scheduled visit, according to the Schedule of Events (specified in Section 9.1 of the protocol). The investigator or designee should query the subject and/or parents/guardians about AEs in general and AEs consistent of COVID-19 and record the information on CRF (see detailed description of the procedure in Section 9.2.2.2 of the protocol).

(a) If the positive RT-qPCR result is from a scheduled visit for sample collection, the next weekly visit will occur as planned. (b) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) but within the window (±3 days) of the next weekly visit, this visit will be recorded as the scheduled next weekly visit. (c) If the positive RT-qPCR result is from an unscheduled sample collection (eg, between scheduled visits) and not within the window (±3 days) of the next weekly visit, this visit will be recorded as an unscheduled visit, and the next weekly visit will occur as planned.

5. Visit may occur by phone or electronic means
6. Sample for diagnostic assay for SARS-CoV-2 (local lab) (see Section 9.2.1.2 of the protocol) and RT-qPCR (NP swab; central lab) should be collected before administration of study drug. Samples for RT-qPCR (NP swab) will be collected by swabbing a single nostril (see Section 9.2.2.1 of the protocol). The remnant samples may additionally be used for exploratory viral RNA sequencing and viral infectivity analyses. The requirement for a local diagnostic assay for SARS-CoV-2 may be waived if the results are not expected to be available in a timely manner for randomization.
7. Study drug should be administered after all biological samples at screening/baseline have been collected.
8. Pediatric subjects who are RT-qPCR positive at the end of the EAP will continue to have samples collected weekly (NP swab; central lab) for RT-qPCR. Pediatric subjects will continue assessments/sample collections until 2 negative RT-qPCR test results have been obtained ≥24 hours apart (all samples must be negative). Subjects who are RT-qPCR negative at the end of the EAP will have samples collected only if they become symptomatic with COVID-19 in the follow-up period.
9. All other pediatric subjects (subset 5) will have additional safety monitoring on day 1 at baseline and 1 hour after study drug administration. All pediatric subjects or their parent/guardian will be advised to call the site if signs/symptoms of injection site or hypersensitivity reactions occur. If the pediatric subject experiences a true medical emergency, they and their parent/guardian should visit their local hospital ED and contact the site personnel later.
10. The investigator may perform a targeted physical exam, request an exam and/or vital signs at any time. These assessments can be performed using a clinic visit or a remote visit with the investigator or sub-investigator, or designee (ie, nurse practitioner in countries where allowed by local law).

11. For all girls at or beyond menarche. If the local urine pregnancy test is positive, the site must perform a serum pregnancy test for confirmation.
12. Samples for drug concentration, immunogenicity, laboratory testing, serology, [redacted] will be collected based on the pediatric subject subset designation as indicated in Table 9 .
13. The serology test results will not be communicated to the sites. The sponsor's blinded study team will not have access to post-baseline results associated with pediatric subject identification until after the database is locked.
14. During each scheduled or unscheduled visit/contact, the investigator or designee will query the pediatric subject and/or parent/guardian about AEs in general (see Section 10 of the protocol) and evaluate if the AEs are associated with SARS-CoV-2 infection (see Section 9.2.2.2. of the protocol). Pediatric subjects and/or parent/guardian with symptomatic SARS-CoV-2 infection should be queried on their symptoms weekly until symptoms resolve, even during follow-up period, then follow the regular schedule.
15. The information for the household assessment, including household members who received EUA approved monoclonal antibody treatment for COVID-19 or household members participating in the R10933-10987-COV-2067 study should preferably be collected at the baseline visit. There will be a follow-up assessment at day 29.
16. All pediatric subjects will have a weekly NP swab sample collected during the EAP. Only pediatric subjects who are RT-qPCR positive will continue to have weekly NP swab samples collected during the follow-up period until 2 consecutive negative (≥24 hr) RT-qPCR results or the end of study visit.
17. Only for RT-qPCR positive subjects (cohort A1 and cohort B1): Complete assessments from the time the subject first becomes RT-qPCR positive or from the time they develop symptoms suspected to be COVID-19 (later confirmed by RT-qPCR positive results) until the subject has had 2 negative tests or COVID-19 related symptoms have resolved (whichever lasts longer), or until the end of study visit.
18. All pediatric subjects and/or parent/guardian will complete the TEAE assessment weekly during the EAP. Subjects who are RT-qPCR negative will complete the TEAE assessment monthly during the follow-up period. Pediatric subjects and/or parent/guardian who have symptomatic SARS-CoV-2 infection will complete the TEAE assessment weekly during the follow-up period until the COVID-19 related symptoms resolve after which the pediatric subject and/or parent/guardian will complete the TEAE assessment monthly until the end of study visit.

[redacted]

Table 9: Schedule of Events: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing

Samples for drug concentration (PK), immunogenicity assessment (ADA), and clinical laboratory testing (hematology, blood chemistry, and serology) will be collected based on subset designation and sample schedule (A, B, C, D) using subject number (assigned by IWRS):

- **Pediatric sentinel group (Subset 4)**: First 12 pediatric subjects (4 subjects per weight group (≥20 kg; 10 kg to <20 kg; <10 kg)
- **All other pediatric subjects (Subset 5):** All other pediatric subjects

Visit	Screening / Baseline[1]	Sentinel Group Only	Efficacy Assessment Period (EAP)			Follow-up Period							ET Visit[5]	Unscheduled Visit
Site (S)	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**			
Visit Number	**1**	**2**	**5**	**6**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**EOS 15**		
Day	1	2	8	15	29	57	85	113	141	169	197	225		
Week	0	0	1	2	4	8	12	16	20	24	28	32		
Window (day)		+2	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Sentinel Group (Subset 4)														
PK-ADA[2,3,9]; Hematology[4]; Blood Chemistry[4], Serology[4,8]														
Schedule A	X[1,8]	X			X[8]								X	X[6,7]
All other subjects (Subset 5)														
PK-ADA[2,3,9]; Hematology[4], Blood Chemistry[4], Serology[8]														
Schedule A	X[1,8]	X			X[8]								X	X[6,7]
Schedule B	X[1,8]		X		X[8]								X	X[6,7]
Schedule C	X[1,8]			X	X[8]								X	X[6,7]
Schedule D	X[1,8]				X[8]			X[8]					X	X[6,7]
[redacted]														
[redacted]	[redacted]													
[redacted]	[redacted]													

ADA, anti-drug antibodies; EAP, Efficacy assessment period; EOS, end of study; ET, Early termination; PK, Pharmacokinetics

10.2.4. Schedule of Events Table 6: Cohorts A1 and B1 (Pediatric Subjects [<12 years]) for Drug Concentration, Immunogenicity, and Laboratory Testing

1. Samples should be collected before the administration of study drug. Administration of study drug must be performed on the on same day as sample collection.
2. Actual dosing time and sample collection times will be recorded for PK-ADA samples.
3. At the screening/baseline visit, the window for baseline pre-dose PK-ADA sample collection is as close to administration of study drug as is reasonable.
4. Whole blood samples for hematology and blood chemistry will be analyzed at central lab.
5. Pediatric subjects who prematurely discontinue the study should have sample collection listed in the ET visit before exiting the study.
6. A PK-ADA serum sample will be collected as soon as possible or within 7 days of receiving the first positive SARS-CoV-2 RT-qPCR result for cohort A pediatric subjects.
7. A PK-ADA serum sample will be collected as soon as possible or within 7 days of first new positive SARS-CoV-2 RT-qPCR result after achieving 2 consecutive negative results for all pediatric subjects.
8. Serum samples for serology will be collected at baseline and day 29. For pediatric subjects <10 kg, the serum sample for serology on the day 29 visit will not be collected due to restrictions in total blood volumes collection. For pediatric subjects <3 kg, the serum sample for serology on the baseline and day 29 visit will not be collected due to restrictions in total blood volumes collection.
9. The PK-ADA serum samples may be analyzed for ADA and NAb, if feasible.

[redacted]

10.2.5. Early Termination Visit

Subjects who are withdrawn from the study will be asked to provide final blood samples for drug concentration and immunogenicity analysis.

10.2.6. Unscheduled Visits

All attempts should be made to keep subjects on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, for SARS-CoV-2 RT-qPCR and serology testing when subjects experience symptoms consistent with SARS-CoV-2 infection (per the broad-term list specified in Section 9.2.2.2 of the protocol), or for any other reason, as warranted.

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV For Studies in healthy subjects only	Comments
Clinical chemistry		
ALT	>3 and ≤5 ULN and baseline ≤3 ULN >5 and ≤10 ULN and baseline ≤5 ULN >10 and ≤20 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Each category is calculated independently.
AST	>3 and ≤5 ULN and baseline ≤3 ULN >5 and ≤10 ULN and baseline ≤5 ULN >10 and ≤20 ULN and baseline ≤10 ULN >20 ULN and baseline ≤20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Each category is calculated independently.
Alkaline Phosphatase	>1.5 ULN and baseline ≤1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L.
Total Bilirubin	>1.5 and ≤2 ULN and baseline ≤1.5 ULN >2 ULN and baseline ≤2.0 ULN	Must be expressed in ULN, not in μmol/L or mg/L.
Conjugated bilirubin	>35% Total Bilirubin and TBILI >1.5 ULN, and baseline Total Bilirubin ≤35% or TBILI ≤1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis
ALT and Total Bilirubin	ALT>3 ULN and TBILI >2 ULN, and baseline ALT ≤3 ULN or TBILI ≤2ULN	
CPK	>3 and ≤10 ULN and baseline ≤3ULN >10 ULN and baseline ≤10ULN	
Creatinine	≥150 μmol/L (Adults) or ≥ULN (if ULN ≥150 μmol/L) and baseline <150 μmol/L or <ULN (if ULN ≥150 μmol/L) ≥30% change from baseline ≥100% change from baseline	3 independent criteria
Creatinine Clearance (Cockcroft's formula)	<15 ml/min and baseline ≥15 ml/min (end stage renal impairment) ≥15 to <30 ml/min and baseline ≥30 ml/min (severe renal impairment) ≥30 to < 60 ml/min and baseline ≥60 ml/min (moderate renal impairment) ≥60 to < 90 ml/min and baseline ≥90 ml/min (mild renal impairment)	Four independent criteria

Parameter	**PCSV** **For Studies in healthy subjects only**	**Comments**
Uric Acid Hyperuricemia: Hypouricemia:	>408 µmol/L or >ULN (if ULN ≥408 µmol/L) and baseline ≤408 µmol/L or ≤ULN (if ULN ≥408 µmol/L) <120 µmol/L or <LLN (if LLN ≤120 µmol/L) and baseline ≥120 µmol/L or ≥LLN (if LLN ≤120 µmol/L)	Two independent criteria
Blood Urea Nitrogen	≥17 mmol/L or ≥ULN (if ULN ≥17 mmol/L) and baseline <17 mmol/L or <ULN (if ULN≥17 mmol/L)	Two independent criteria
Chloride Hypochloremia: Hyperchloremia:	<80 mmol/L or <LLN (if LLN ≤80 mmol/L) and baseline ≥80 mmol/L or ≥LLN (if LLN ≤80 mmol/L) >115 mmol/L or >ULN (if ULN ≥115 mmol/L) and baseline ≤115 mmol/L or ≤ULN (if ULN ≥115 mmol/L)	Two independent criteria
Sodium Hyponatremia: Hypernatremia:	≤129 mmol/L or ≤LLN (if LLN ≤129 mmol/L) and baseline >129 mmol/L or >LLN (if LLN ≤129 mmol/L) ≥160 mmol/L or ≥ULN (if ULN ≥160 mmol/L) and baseline <160 mmol/L or <ULN (if ULN ≥160 mmol/L)	Two independent criteria
Potassium Hypokalemia Hyperkalemia	<3 mmol/L or <LLN (if LLN ≤3 mmol/L) and baseline ≥3 mmol/L or ≥LLN (if LLN ≤3 mmol/L) ≥5.5 mmol/L or ≥ULN (if ULN ≥5.5 mmol/L) and baseline <5.5 mmol/L or <ULN (if ULN ≥5.5 mmol/L)	Two independent criteria
Total Cholesterol	≥7.74 mmol/L or ≥ULN (if ULN ≥7.74 mmol/L) and baseline <7.74 mmol/L or <ULN (if ULN ≥7.74 mmol/L)	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L or ≥ULN (if ULN ≥4.6 mmol/L) and baseline <4.6 mmol/L or <ULN (if ULN ≥4.6 mmol/L)	Threshold for therapeutic intervention

Parameter	PCSV For Studies in healthy subjects only	Comments
Glucose Hypoglycemia Hyperglycemia	 ≤3.9 mmol/L and <LLN and baseline >3.9 mmol/L or ≥ LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted) and baseline <11.1 mmol/L (unfasted); <7 mmol/L (fasted)	
HbA1c	>8% and baseline ≤ 8%	
Albumin	≤25 g/L or ≤LLN (if LLN≤25 g/L) and baseline >25 g/L or >LLN (if LLN ≤25 g/L)	
CRP	>2 ULN or >10 mg/L (if ULN not provided) and baseline ≤2 ULN or ≤10 mg/L (if ULN not provided)	
Hematology		
WBC	<3.0 Giga/L or <LLN (if LLN ≤3.0 Giga/L) and baseline ≥3.0 Giga/L or ≥LLN (if LLN≤3.0 Giga/L) (Non-Black); <2.0 Giga/L or <LLN (if LLN ≤2.0 Giga/L) and baseline ≥2.0 Giga/L or ≥LLN (if LLN≤2.0 Giga/L) (Black) ≥16.0 Giga/L or ≥ULN (if ULN ≥16.0 Giga/L) and baseline < 16 Giga/L or <ULN (if ULN ≥16.0 Giga/L)	
Lymphocytes	>4.0 Giga/L or >ULN (if ULN ≥4.0 Giga/L) and baseline ≤4.0 Giga/L or ≤ULN (if ULN ≥4.0 Giga/L)	
Neutrophils	<1.5 Giga/L or <LLN (if LLN ≤1.5 Giga/L) and baseline ≥1.5 Giga/L or ≥LLN (if LLN ≤1.5 Giga/L) (Non-Black); <1.0 Giga/L or <LLN (if LLN ≤1.0 Giga/L) and baseline ≥1.0 Giga/L or ≥LLN (if LLN ≤1.0 Giga/L) (Black)	
Monocytes	>0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L) and baseline ≤0.7 Giga/L or ≤ULN (if ULN ≥0.7 Giga/L)	

Parameter	PCSV For Studies in healthy subjects only	Comments
Basophils	>0.1 Giga/L or >ULN (if ULN ≥0.1 Giga/L) and baseline ≤0.1 Giga/L or ≤ULN (if ULN ≥0.1 Giga/L)	
Eosinophils	>0.5 Giga/L or >ULN (if ULN ≥0.5 Giga/L) and baseline ≤0.5 Giga/L or ≤ULN (if ULN ≥0.5 Giga/L)	
Hemoglobin	≤115 g/L or ≤LLN (if LLN ≤115 g/L) and baseline >115 g/L or >LLN (if LLN ≤115 g/L) for male; ≤95 g/L or ≤LLN (if LLN ≤95 g/L) and baseline >95 g/L or >LLN (if LLN ≤95 g/L) for Female. ≥185 g/L or ≥ULN (if ULN ≥185 g/L) and baseline <185 g/L or <ULN (if ULN ≥185 g/L) for Male; ≥165 g/L or ≥ULN (if ULN ≥165 g/L) and baseline <165 g/L or <ULN (if ULN ≥165 g/L) for Female Decrease from Baseline ≥20 g/L	Three criteria are independent.
Hematocrit	≤0.37 v/v or ≤LLN (if LLN ≤0.37 v/v) and baseline >0.37 v/v or >LLN (if LLN ≤0.37 v/v) for Male; ≤0.32 v/v or ≤LLN (if LLN ≤0.32 v/v) and baseline > 0.32 v/v or >LLN (if LLN ≤0.32 v/v) for Female ≥0.55 v/v or ≥ULN (if ULN ≥0.55 v/v) and baseline <0.55 v/v or <ULN (if ULN ≥0.55 v/v) for Male; ≥0.5 v/v or ≥ULN (if ULN ≥0.5 v/v) and baseline < 0.5 v/v or <ULN (if ULN ≥0.5 v/v) for Female	Two Criteria are independent
RBC	≥6 Tera/L or ≥ULN (if ULN ≥6 Tera/L) and baseline < 6 Tera/L or <ULN (if ULN ≥6 Tera/L)	
Platelets	<100 Giga/L or <LLN (if LLN ≤100 Giga/L) and baseline ≥100 Giga/L or ≥LLN (if LLN≤100 Giga/L) ≥700 Giga/L or ≥ULN (if ULN ≥700 Giga/L) and baseline <700 Giga/L or <ULN (if ULN ≥700 Giga/L)	Two independent criteria

Parameter	PCSV For Studies in healthy subjects only	Comments
Vital signs		
HR	<45 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	To be applied for all positions except STANDING
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions except STANDING
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions except STANDING

10.4. Example of SAS Procedures for Primary Analysis and Missing Data Imputations by FCS

Primary Analysis - GEE Model

Below is an example of SAS code using a generalized linear model to estimate the odds ratio between the treatment groups with the generalized estimation equation (GEE) approach after 100 imputations.

```
proc genmod data=DATA_IN;
class treatment(ref='0') Age_group region;/*eg.treatment= 0:placebo */
by _imputation_;
model response(event='1') =treatment region age_group/dist=bin link=logit;
repeat subject=household_id/type=cs;
lsmeans treatment/diff om cl ilink;
ods output diffs=logOR geeexchcorr=icc;
run;
```

Primary Analysis - Logistic Regression Model

Below is an example of SAS code using a logistic regression model instead of using GEE approach when the percentage of households with a single study subject is 70% or more to estimate the odds ratio between the treatment groups after 100 imputations.

```
proc genmod data=DATA_IN descending;
class treatment(ref='0') Age_group region;
by _imputation_;
model response(event='1') =treatment region age_group/dist=bin link=logit;
lsmeans treatment/diff om cl ilink;
ods output diffs=logOR ParameterEstimates=parameterestimates;
```

```
run;
```

Missing Data Imputations – FCS

Assume the missing RT-qPCR test results occurred across Visit 5 (Day 8) to Visit 8 (Day 29) (e.g. 1=positive vs 0=negative). An example of SAS code for FCS MI with the random seed=2069 is presented below.

```
proc mi data=DATAIN out=DATAOUT seed=2069 nimpute=100;
class treatment age_group   region v5 v6 v7 v8;
var treatment age_group region v5 v6 v7 v8;
fcs logistic(v5/LIKELIHOOD=AUGMENT);
fcs logistic(v6/LIKELIHOOD=AUGMENT);
fcs logistic(v7/LIKELIHOOD=AUGMENT);
fcs logistic(v8/LIKELIHOOD=AUGMENT);
run;
```

After FCS MI to generate 100 complete datasets, each subject's overall RT-qPCR test status during the EAP can be determined by any of imputed value V5 to V8 is equal to 1. The same model using GEE approach or logistic regression for the primary analysis will be applied.

The results from the 100 analyses will be combined using Rubin's formulae through PROC MIANALYZE procedure shown below.

```
proc mianalyze data=logOR;
ods output parameterestimates=final_logor;
modeleffects estimate;
stderr stderr;
run;
```

The estimates of log(odds ratio) and the corresponding 95% confidence interval (CI) will be provided in the FINAL_LOGOR dataset. The results of odds ratio and 95% CI will be derived by taking the exponential of these estimates.

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